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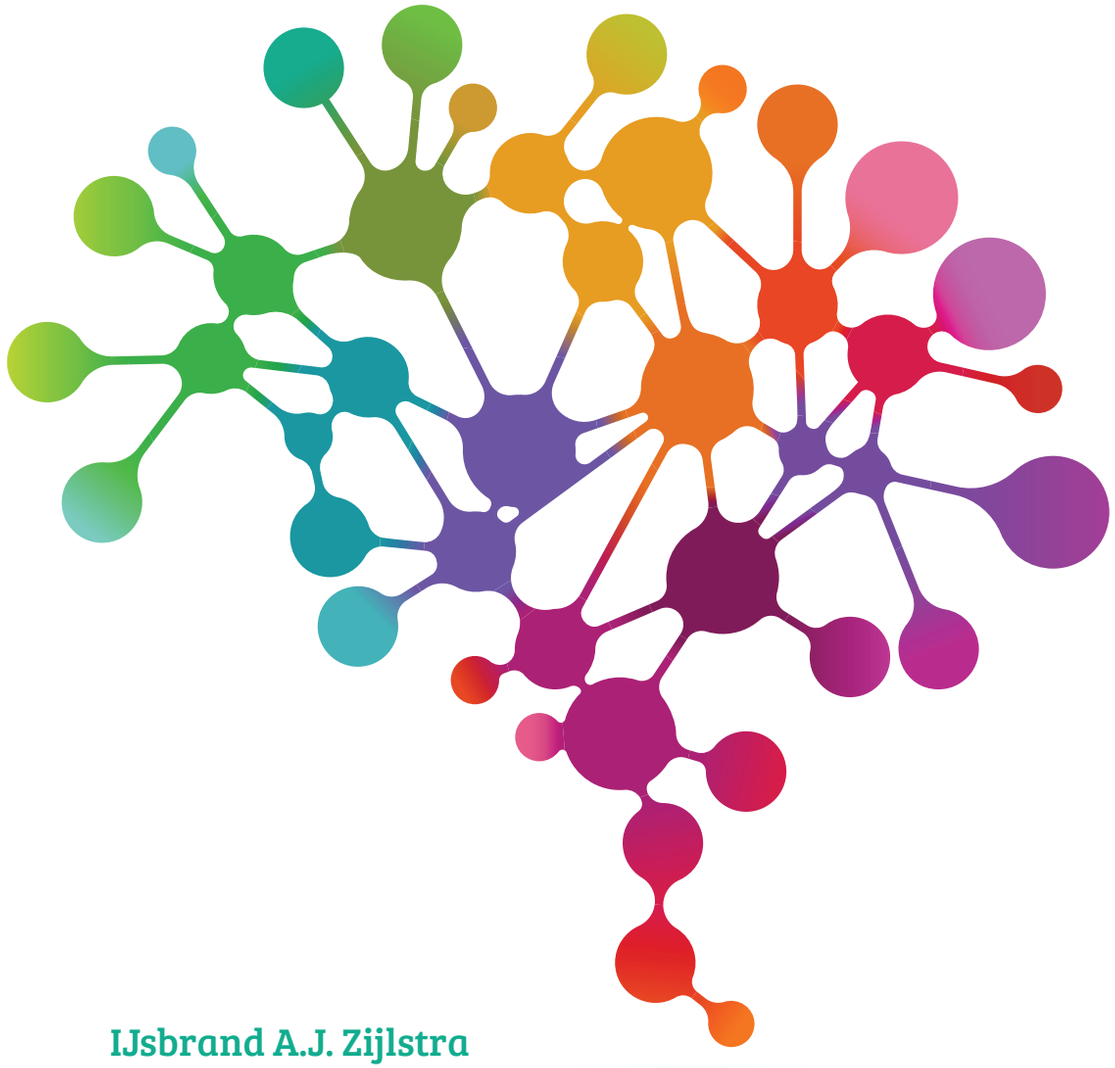

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ADVANCES IN ANEURYSM TREATMENT WITH A FOCUS ON MIDDLE CEREBRAL ARTERY ANEURYSMS AND DELAYED CEREBRAL ISCHEMIA

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
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ten overstaan van een door het College voor Promoties ingestelde commissie,
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door

IJsbrand Andreas Jan Zijlstra
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Contents

1.

General introduction and outline of the thesis

Subarachnoid hemorrhage (SAH) occurs in about 1,500 cases per year in the Netherlands. Most patients are relatively young with a mean age on admission of 55 years. The main symptom is very severe headache that reaches its maximum in a few seconds to minutes and holds on for at least an hour. Almost half of the patients is unconscious after a SAH. In the majority of cases the subarachnoid hemorrhage is caused by an intracranial aneurysm.[1] The most frequent locations for intracranial aneurysms are the anterior and posterior communicating arteries and the middle cerebral artery (Figure 1.1).[2] Genetic predisposal (e.g. familial aneurysms, ADPKD and Marfan's disease), female gender, smoking, hypertension and old age are risk factors for aneurysm development. Histopathologically vascular remodeling (e.g. smooth muscle cell apoptosis and degradation of the extracellular matrix) and inflammation play an important role in the pathogenesis of intracranial aneurysms.[3] One possible hemodynamic factor that can play a role in the cascade of the pathogenesis of intracranial aneurysms is wall shear stress on branching points of the intracranial arteries.[4,5] Among the predictors for aneurysm rupture and thus aneurysmal SAH (aSAH) are: the population the patient lives in (the incidence differs

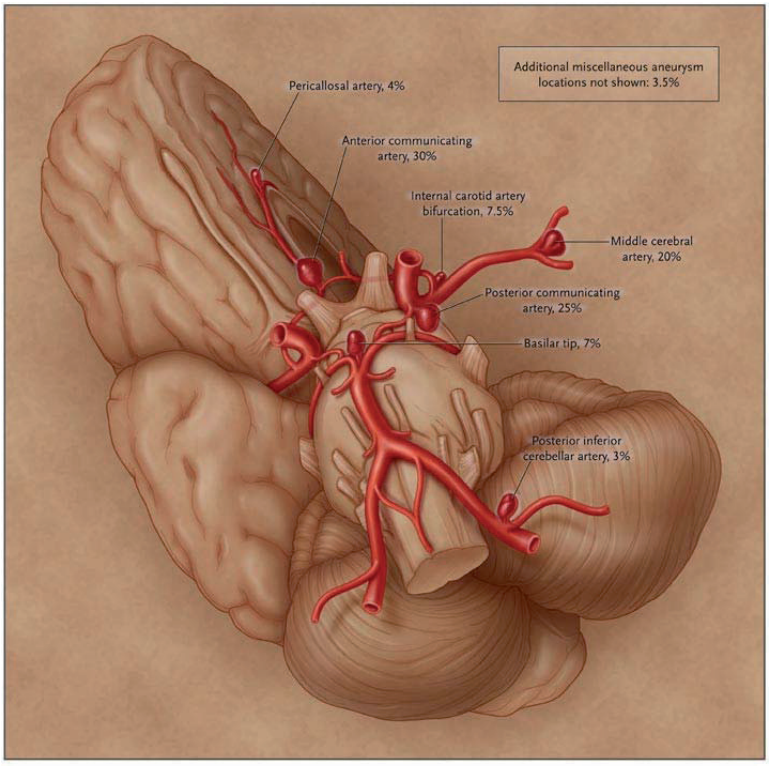

Figure 1.1. The intracranial vasculature, showing the most frequent locations of intracranial aneurysms. Reproduced with permission from (Brisman et al. NEJM 2006), Copyright Massachusetts Medical Society. Percentages indicate the incidence of intracranial aneurysms.

between geographical areas)), hypertension, age > 70 years, aneurysm size > 7 mm, location on the anterior communicating artery or on the posterior circulation, and history of SAH.[6]

Imaging

In every patient who is admitted on suspicion of a SAH, a non-contrast computed tomography (NCCT)scan is made to detect the hemorrhage. This NCCT-scan can also be used to determine the hemorrhage volume, the midline shift and the presence of hydrocephalus. When the SAH is confirmed, a CT-angiography (CTA)with intravenous administration contrast agent (or a Magnetic resonance angiography(MRA)) is made to find the cause of the SAH. A SAH can be aneurysmal or non-aneurysmal. Possible causes of non-aneurysmal SAH are (among others): arteriovenous malformation (AVM), trauma, reversible cerebral vasoconstriction syndrome (RVCS). In case of an aSAH the CTA can show the location and anatomical configuration of the causative aneurysm. When no cause of the SAH is found with CTA, a digital subtraction angiography with 3 dimensional rotational angiography (3DRA) can be made additionally.[7] This DSA with 3DRA can also be used to determine whether the aneurysm is suitable for treatment with endovascular coiling or not. In case multiple aneurysms are found, the blood distribution pattern on NCCT combined with the aneurysm location and anatomical configuration can be useful in trying to detect the causative aneurysm. When the NCCT shows no subarachnoid hemorrhage, a lumbar puncture is performed a minimum of 12 hours after the SAH ictus to exclude bilirubin in the CSF.[8] The subarachnoid hemorrhage can be graded on a NCCT using the (modified) Fisher score or the Hydra scale. This has shown to have value in the prediction of the occurrence of vasospasm (in that time thought to be cause of delayed cerebral ischemia (DCI)) after aSAH. The Fisher scale is a four-point scale (score 1 = no blood, 4 = intraventricular clot with or without diffuse SAH). The modified 4-point Fisher scale is more accurate in predicting vasospasm, taking thin (< 1 mm) and thick (> 1 mm) cisternal hematoma and ventricular hematoma into account, but this still leaves the interpretation to the physician that reads the CT images. The Hydra scale is a four-point scale (No blood = 0 points, completely filled with blood = 3 points, maximum 30 points), and grades the amount of blood in the basal cisterns, fissures and the fourth ventricle. These scales are rough (modified (Fisher), laborious (Hijdra) and operator-dependent (both)). Studies using these scales have reported on the clinical importance of subarachnoid hemorrhage grading, by showing that more blood after aSAH has a higher association with the occurrence of vasospasm. The next step would be to develop, and validate, an easy to use, accurate, operator-independent automatic quantification method to study the association of real hematoma volume (total and on different locations) after aSAH with DCI.[9-12]

Treatment

When an aneurysm is detected, the best possible treatment option is determined according to the patient's clinical condition and the aneurysm configuration. The aim of the treatment is to prevent the aneurysm from rebleeding. Approximately 90% of the rebleedings occur within 24 hours after the initial bleeding and almost 50% of these rebleedings occur in the first 6 hours making early treatment essential.[13-16] The aneurysm can be treated by neurosurgical (microsurgical clipping, wrapping, bypass construction or by artery occlusion in case of a dissecting aneurysm) or by endovascular treatment (coiling with or without additional devices, or artery occlusion in case of a dissecting aneurysm). The most common treatment nowadays is coiling, whereas microsurgical clipping is reserved for those aneurysms that cannot be coiled. During microsurgical clipping the surgeon performs a craniotomy and places one, or more, titanium clip(s) on the neck of the aneurysm, occluding blood flow into the aneurysm (Figure 1.2). During endovascular coiling access is usually gained from the common femoral artery in the groin (Figure 1.3). The aim of this procedure is to enter the aneurysmal sac with a microcatheter and to fill the aneurysm with platinum coils to stop flow into the aneurysm and to promote thrombus formation.[2] An aneurysm with a small neck, relative to the aneurysm sac, that has no branches coming out of the sac is ideal for endovascular treatment. Besides the

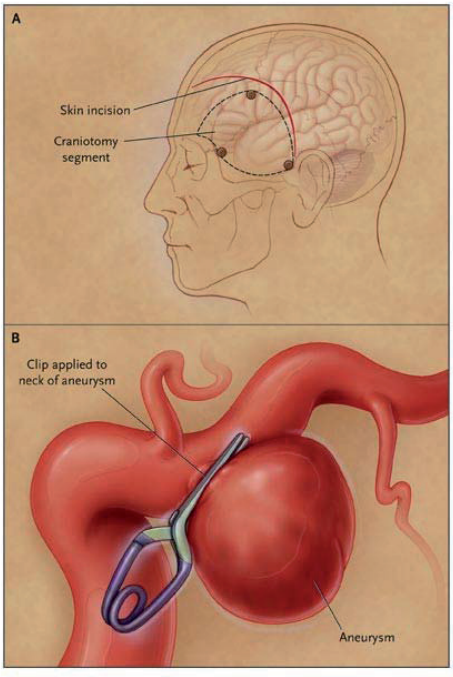

Figure 1.2. Microsurgical clipping with **(A)** outline of skin incision and craniotomy segment and **(B)** application of the clip blade to the neck of the aneurysm. Reproduced with permission from (Brisman et al. NEJM 2006), Copyright Massachusetts Medical Society.

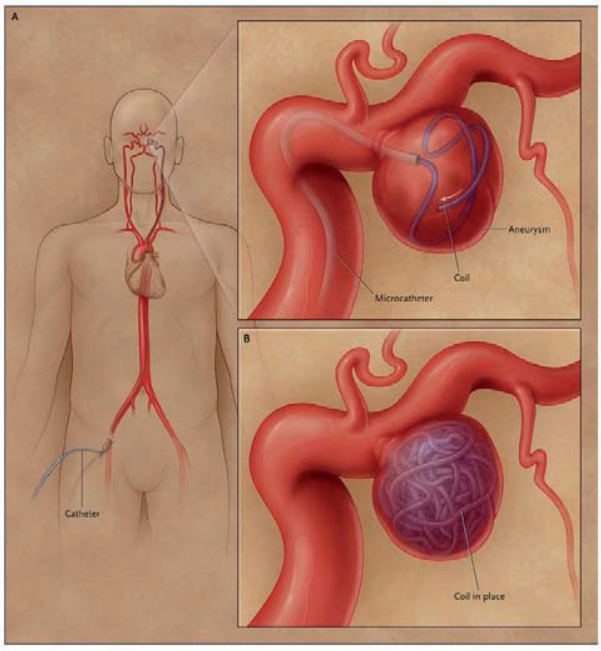

Figure 1.3. Endovascular coiling with **(A)** route from groin to brain and microcatheter in the aneurysm and **(B)** aneurysm occluded with coils. Reproduced with permission from (Brisman et al. NEJM 2006), Copyright Massachusetts Medical Society.

conventional coiling technique, several additional devices (e.g. balloons, stents and web devices) are available to treat aneurysms with a more difficult anatomy endovascularly.[17]

MCA aneurysms

The only randomized trial comparing microsurgical clipping and endovascular coiling in patients with ruptured aneurysms suitable for both treatments is the ISAT trial. Although the ISAT trial showed a benefit for endovascular treatment of ruptured aneurysms on all locations, middle cerebral artery aneurysms were underrepresented, leaving room for discussion on what is the best treatment for MCA aneurysms.[18] One published review on the treatment of MCA aneurysms showed that endovascular treatment is feasible and effective, but that the periprocedural morbidity and mortality was substantial.[19] However, this study did not include studies describing MCA aneurysm treatment outcome in subgroups of the total study population, and did not compare endovascular treatment with surgical treatment. Some authors advocate strict endovascular treatment of all MCA aneurysms, with or without additional devices (balloons and stents) relentless of the higher risk of complications using stents.[20] Others advocate strict surgical treatment also to maintain surgical experience in an era that more and more aneurysm are treated endovascularly.[21] A systematic, extensive review comparing conventional coiling and clipping of MCA aneurysms might help to end this lingering discussion.

MCA aneurysms with concomitant intraparenchymal hematoma

The presence of a concurrent large Sylvian fissure or intraparenchymal hematoma (IPH) after aSAH from an MCA aneurysm can also play a role in the determination of the preferred treatment strategy. The outcome in these patients is worse, with reported mortality rates up to 56% after clipping, with or without clot removal.[22-24] The 2012 American Heart Association guidelines on the management of subarachnoid hemorrhage states that in patients with ruptured MCA aneurysms with large (> 50 ml) hematomas clipping (with hematoma evacuation) might receive increased consideration, although the scientific evidence for this rationale is sparse.[25] The study on clipping with hematoma evacuation that was referred to in this guideline did not define hematoma volume in </> 50 ml.[26] In others studies the hematoma volume is often measured on a NCCT with the ABC/2 method, which is known to overrate the hematoma volume.[27,28] In this specific patient group, there is no literature on the clinical outcome after coiling of the aneurysm combined with surgical clot removal, although papers describing patients with ruptured aneurysms on all locations treated with coiling followed by clot removal report mortality rates of 20–30%.[29-31] One rationale for coiling of the aneurysm prior to clot removal, despite the delay in decompression, is securing the aneurysm to prevent it from rebleeding during the clot removal. While there is no study comparing patients with ruptured MCA aneurysms and concomitant IPH's treated with coiling and clipping, with or without decompression and clot removal, it is still debatable whether patients benefit from early hematoma evacuation and clipping.[22-24] Moreover, there is no study evaluating the role of precisely measured hematoma volume in these patients regarding treatment decision and clinical outcome.

Delayed cerebral ischemia

Besides preventing rebleeding, by early (< 24 hours) aneurysm treatment, and treatment of hydrocephalus, meningitis and seizures, the main goal is to prevent aSAH patients from having delayed cerebral ischemia (DCI), as DCI is the most important complication affecting 20–30% of the aSAH patients and is associated with a poor outcome.[32] Before 2010 there was no uniform definition of DCI. Multiple different terms were used and most clinicians thought that it was solely caused by vasospasm. Since 2010 clinical DCI is defined as the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies. Radiological DCI is defined as the presence of cerebral infarction

on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI.[33] Moreover, while in the past blood-induced vasospasm was thought to be the cause, nowadays DCI is thought to be caused by both cerebral vasospasm and activation of several key pathophysiological pathways, including cortical spreading depolarisations, endothelial dysfunction, microthrombosis and neuroinflammation.[34,35] Currently there is no specific treatment for DCI. Previously promoted therapies like triple H (hypertension induction, hypervolemia and hemodilution), angioplasty and intra-arterial administration of vasodilators (e.g. Papaverine and Verapamil) have not proven to be beneficial on clinical outcome (hypertension induction and angioplasty) or carry a high risk of complications (angioplasty) or have not been studied in a randomized clinical trial (vasodilators).[36-38] Regarding intravascular volume euvolemia is recommended.[39] Furthermore, if the patients' normal tension is known, a mean arterial pressure + 10% is the local target.

Hematoma volume after aSAH and DCI

Blood degradation products in the CSF are thought to play a role in the occurrence of DCI.[40] Several studies have associated the hematoma volume after aSAH with vasospasm (in that time thought to be the cause of DCI), using NCCT grading scales such as the (modified) Fisher or Hijdra scales. These grading scales only provide a rough estimation of the aSAH hemorrhage volume and are observer-dependent, factors that may add to the moderate prediction rates of DCI.[10,11,32,41] More accurate aSAH volume quantification might add to the development of better prediction models for DCI and easier identification of patients at risk for DCI. Besides the total blood volume after aSAH, the hematoma volume on specific locations (cisternal and ventricular) is thought to be associated with the occurrence of vasospasm.[42] There is no study associating the location-specific hematoma volume after aSAH in milliliters with the occurrence of DCI, using automatic quantification and multivariate analysis correcting for possible confounders.

The role of Heparin in DCI prevention

Besides prediction of DCI, the prevention of DCI is an important subject of research in aSAH patients. Every patient admitted to the hospital with aSAH is treated prophylactically for three

weeks with Nimodipine, a calcium channel blocker. This does not reduce the occurrence of DCI, but has been shown to have a beneficial effect on the clinical outcome, by reducing the occurrence of vasospasm and ischemia.[1,43] Prevention of DCI by administration of low-molecular-weight heparin (LMWH) or unfractioned heparin after aneurysm treatment has been studied as heparin might antagonize multiple physiological mechanisms that contribute to the development of DCI.[44] For instance, treatment with low-dose heparine has shown a reduction in neuroinflammation (one of the possible causes of DCI) and transsynaptic apoptosis in rats with induced ischemia.[45] Another study showed a reduction in brain edema and improvement in motor and cognitive impairment in rats with induced traumatic brain injury after treatment with heparin. Studies in aSAH patients have shown ambiguous results of subcutaneous (LMWH) or intravenous (unfractioned) administration of low-dose heparin after surgical or endovascular aneurysm treatment.[46-48] Whether administration of high dose LMWH has more beneficial or potential harmful effects than administration of low-dose LMWH after endovascular aneurysm treatment in aSAH patients has not been studied. Moreover, no study has compared the administration of low- and high-dose LMWH in aSAH patients after aneurysm treatment and the possible effects on the occurrence of DCI and clinical outcome.

Clinical outcome

Aneurysmal SAH (aSAH) has a high case fatality of up to 30% of the patients, even after intensive treatment.[49] Only one third of the patients are independent in their daily activities after aSAH treatment and only one sixth of the patients are able to perform the same job as before the hemorrhage.[1] Factors contributing to worse clinical outcome are poor neurological status on admission, rebleeding, delayed cerebral ischemia (DCI), hydrocephalus and meningitis.[50] The neurological status on admission can be scored with the World Federation of Neurosurgical Societies (WFNS) scale, which is a 5-point scale that combines the 15-point Glasgow coma scale (GCS) with neurological deficits.[51] One of the possible factors that contribute to poor neurological status on admission is the amount of extravasated blood, leading to raised intracranial pressure and hydrocephalus. Clinical outcome after aSAH can be measured with the modified Rankin scale. This a six point scale measuring the functional (in)dependency of patients after SAH, based on the ability to perform normal daily activities (0 = no symptoms at all, 6 = death).[52] A similar scale, also often used, is the five point Glasgow Outcome Scale (GOS) (1 = death, 5 = low disability).[53]

Aims and outline of this thesis

This thesis describes different aspects of aneurysmal SAH treatment with a focus on middle cerebral artery aneurysms and delayed cerebral ischemia.

The main objectives are:

- To review the literature on the topic of clinical and imaging outcome of patients after clipping or (conventional) coiling of (un)ruptured middle cerebral artery aneurysms;
- To retrospectively study whether the volume of intraparenchymal hematomas after aSAH of MCA aneurysms is associated with poor clinical outcome, and whether there is a difference in clinical outcome after clipping and coiling, with or without clot removal;
- To validate an automatic aSAH volume quantification method;
- To study the association of the (total and location-dependent) quantified SAH volume after aSAH with the occurrence of DCI;
- To study the difference in clinical outcome and the occurrence of DCI in patients receiving different doses of Nadroparin after endovascularly treated aneurysms.

In **Chapter 2** we set out to perform a systematic review on the clinical and imaging outcome of the treatment of patients with a middle cerebral artery (MCA) aneurysm, as there is an ongoing debate on what is the best treatment for patients with an MCA aneurysm. The study in **Chapter 3** was performed because the 2009 ASA guidelines state that microsurgical clipping is preferred in patients with hematoma volumes of > 50 ml, while there hardly is a scientific basis for this statement. Moreover, this is not the current practice in the AMC hospital and is not mentioned in the Dutch guidelines on subarachnoid hemorrhage, possibly while there is no scientific evidence. We wanted to assess the possible association between intraparenchymal hematoma volume (< or > 50 ml), neurological condition on admission, and any combination of treatment options (no treatment, coiling or clipping, decompression and clot removal) and clinical outcome. In **Chapter 4** we aimed to develop, and validate, an accurate, operator-independent subarachnoid hemorrhage quantification method, using the non-contrast CT (NCCT)scans of patients with a ruptured MCA aneurysm, as aSAH grading has been shown to be clinically important, but until now has been done with operator-dependent, rough and/or laborious grading methods. In **Chapter 5** we used the newly developed, and validated, quantification method to test the hypothesis that the total hemorrhage volume in ml after aneurysmal SAH (aSAH) was associated with the occurrence of delayed cerebral ischemia (DCI). We used multivariate analysis, correcting for confounders, with accurate and operator-independent hematoma grading as a possible add-on in prediction models of DCI. In **Chapter 6** we aimed to find out whether there was an association between the exact location-specific

hematoma volume in ml and the occurrence of DCI, for the same reasons as we performed the study described in Chapter 5. In **Chapter 7** we studied whether there was a benefit for patients receiving high-dose Nadroparin versus patients receiving low-dose Nadroparin regarding the occurrence of DCI and clinical outcome, as there is an ongoing debate, and hardly any literature, on the best anticoagulation therapy after aSAH aneurysm treatment, and on the possible beneficial effects of anticoagulants on the occurrence of DCI and clinical outcome. In **Chapter 8** the main findings of this thesis are discussed, and recommendations for future research are proposed.

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2.

Coiling and clipping of middle cerebral artery aneurysms: a systematic review on clinical and imaging outcome

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Abstract

Background: There is an ongoing debate on the preferred treatment of middle cerebral artery (MCA) aneurysms. The purpose of this study was to assess the clinical and imaging outcomes comparing conventional coiling and clipping of unruptured and ruptured MCA aneurysms.

Methods: We searched the electronic databases PubMed, EMBASE, and Cochrane from January 1990 to May 2014.

Results: 51 studies were included in the analysis. Favorable outcome was reported in 97.0% and 77.1%, and in 97.2% and 72.8% of patients after coiling and clipping of unruptured and ruptured aneurysms, respectively. Death rates were 1.1% and 8.4% after coiling and 0.3% and 14.7% after clipping of unruptured and ruptured aneurysms, respectively. Initial adequate occlusion was obtained in 89.6% and 92.1% after coiling of unruptured and ruptured aneurysms, respectively. Only three studies on clipping reported on aneurysm occlusion during follow-up.

Conclusions: Both coiling and clipping are procedures with low mortality and morbidity rates and, although it may seem that coiling is better for ruptured aneurysms and clipping for unruptured aneurysms, no firm conclusions can be drawn due to the variation in study design and lack of standardized reporting on MCA aneurysm treatments. Standardized observational studies from prospectively kept databases are needed to allow stronger conclusions to be drawn on what is the best treatment for MCA aneurysms. Comparable with aneurysms in other locations, a multidisciplinary approach is therefore recommended with selection of treatment modality based on the clinical condition of the patient and the morphological aspects of the aneurysm.

Introduction

The International Subarachnoid Aneurysm Trial (ISAT) showed better independent survival at 1 year for patients with coiled ruptured intracranial aneurysms compared with clipping, but middle cerebral artery (MCA) aneurysms were relatively underreported.[1] A recent systematic review showed that endovascular treatment of MCA aneurysms is feasible and effective in selected cases, but the peri-procedural mortality and morbidity are not negligible, and studies in which MCA aneurysms were described as a subgroup of a total study population were not included.[2] Another recent review favoring clipping of unruptured aneurysms also included papers solely reporting on stent assisted coiling or endovascular treatment of complex aneurysms, which are procedures which carry a higher risk of complications.[3] It is therefore not surprising that the debate on the preferred treatment modality for MCA aneurysms continues. A worrying side effect of this lingering controversy is that individual patients do not always receive the best possible treatment, but are sometimes operated on only to maintain surgical experience or, in contrast, aneurysms are being stented and coiled when there is no neurosurgical backup.[4,5]

The purpose of this systematic review is to assess the clinical and imaging outcome rates of coiling and clipping of unruptured and ruptured MCA aneurysms during follow-up.

Methods

Literature search

We searched the electronic databases PubMed, EMBASE, and Cochrane from January 1990 to May 2014. The key words and MESH terms 'intracranial aneurysm*', 'mca', 'middle cerebral artery aneurysm*', 'coil/coils/coiling', 'clipping/clip ligation/clip application/clip reapplication', and 'endovascular procedures/endovascular embolization/ embolization/therapeutic/therapeutic embolization', were used in relevant combinations. The search was restricted to human studies in English, German, and Dutch. After combining the results, cross referencing was performed to search for additional studies.

Eligibility criteria

Two authors (IJAZ and RvdB) screened all titles and abstracts for eligible studies. Studies describing patients with MCA aneurysms, both as the total patient sample or as a subgroup, were selected based on the following inclusion criteria: the study described more than 10 patients with either coiled or clipped MCA aneurysms; and the study reported at least one of

the following items for the group of MCA patients—death, clinical status during follow-up, or follow-up imaging (DSA, MR angiography, or CT angiography) with aneurysm occlusion grade and/or retreatment rates.

Studies in which different aneurysm types were described and analyzed, such as complex, fusiform, giant, or mycotic aneurysms were included only when these aneurysms were subject to regular coil or clip treatment. This meant that series with parent vessel occlusion and more complex techniques, such as bypass surgery or flow diverters, which are usually reserved for more specialized, high volume centers, were excluded. Studies focused on stent assisted or balloon assisted coiling were also not included in this review for the same reason.

Studies without specific MCA data, case reports, book chapters, conference abstracts, comments, letters, reviews, and studies in children (<18 years) with aneurysms were excluded. In studies with overlapping data cohorts, we selected the study with the largest sample size or the most relevant data. Full papers were independently evaluated by two authors (IJAZ and RvdB). In the case of disagreement with respect to eligibility, consensus was reached.

Data extraction

One author (IJAZ) extracted and processed the relevant data according to the PRISMA statement.[6] Data on the total number of (patients with) MCA aneurysms, coiled/clipped aneurysms, and ruptured/unruptured aneurysms were extracted. Furthermore, clinical data were extracted including neurological status on admission, death, cause of death, clinical status during follow-up, intraprocedural ruptures, ischemia, post-treatment hemorrhages, and time to clinical follow-up.

Neurological status on hospital admission was extracted if measured by the World Federation of Neurological Society subarachnoid hemorrhage grading scale (WFNS) or the Hunt and Hess score (HH).[7,8] Ischemia was defined as thromboembolic periprocedural complications, ischemia on imaging, or clinical ischemia. Clinical status during follow-up was extracted if measured by the modified Rankin Scale (mRS) or the Glasgow Outcome Scale (GOS).[9,10] In concordance with other studies, we defined a favorable clinical outcome as a modified Rankin Scale score of 0–2 or a GOS score of 4–5 (French GOS).[11] All other outcomes, including death, were considered unfavorable.

Imaging follow-up data included time to imaging during follow-up, occlusion rate, and retreatment rate. Completely occluded aneurysms and aneurysms with a neck remnant were considered adequately occluded.[12] If the data were unclear, the authors were contacted for additional information.

Assessment of quality

The Newcastle–Ottawa quality assessment scale for cohort studies (NOS Scale) and the Cochrane Collaboration's risk of bias assessment tool for randomized trials were used to assess the risk of bias.[13,14] The assessment was done independently by two authors (IJZ and DV). As there were no studies in this review comparing cohorts, both the items 'selection of the non-exposed cohort' and 'comparability' of the NOS Scale were not applicable and therefore excluded from the scale for this study. These modifications resulted in a maximum score of 6 points instead of 9. Follow-up was considered adequate when clinical and imaging follow-up was performed in 80% or more of the included patients. Follow-up was considered long enough if it was performed at least 3 months after baseline. In the case of disagreement between authors with respect to risk of bias scores, consensus was reached.

Data analysis

When possible, clinical outcome data were reported in four sub-groups: coiled unruptured aneurysms, coiled ruptured aneurysms, clipped unruptured aneurysms, and clipped ruptured aneurysms. Where possible, imaging outcome for coiled aneurysms was divided between ruptured and unruptured aneurysms.

Percentages for the different clinical outcome items were calculated based on the number of patients eligible for the specific item. Percentages for imaging outcome items were calculated based on the number of aneurysms eligible for the specific item. Mean percentages and 95% CIs were calculated for all outcomes.

Results

Search results

The search yielded 11 598 studies. After removing 3913 duplicates, 7685 studies remained (Embase 2570, Pubmed 4923, and Cochrane 192— Figure S2.1 in supplementary appendix). After screening titles and/or abstracts, 7449 studies were excluded, leaving 236 full text papers for review. Finally, 51 studies were included in the analysis (Tables 2.1 and 2.2; references in supplementary appendix).

The most frequent reasons for exclusion were no (clear) description of MCA outcome data and too small sample size.

Table 2.1. Baseline characteristics of included studies on patients with MCA aneurysms

Study No	Author	Year	NOS scale score‡	Coil unruptured patients†	Coil ruptured patients†	Clip unruptured patients†	Clip ruptured patients†	Cinical outcome score	FU period clinical (months)	FU period Imaging (months)
1	Abla*	2013	3	19	14	0	0	mRS	0–49	0–49
2	Aghakani	2008	3	0	0	117	0	mRS	10	NR
3	Aikawa	2007	5	0	26	0	0	mRS	NR	NR
4	Bracard*	2010	4	67	73	0	0	GOS	0–12	0–12
5	Brinjiki	2011	3	26	6	0	0	mRS	NR	0–3
6	Cho*	2013	2	55	5	0	0	GOS	0	6
7	Choi	2012	3	0	0	125	0	mRS	3–62	0–1.5
8	Chyatte	2011	2	0	0	44	17	mRS	6	NR
9	Deng	2007	3	0	12	0	0	NR	TD	TD
10	Diaz	2014	3	40	10	25	9	mRS	6	0–62
11	Dijk van*	2011	3	0	0	27	75	mRS	2	NR
12	Doerfler	2006	4	16	15	0	0	GOS	6	6
13	Flamm	2000	2	0	0	93	0	Death	NR	NR
14	Guglielmi	2008	1	52	61	0	0	Death	NR	NR
15	Ha	2011	4	0	0	21	28	GOS	6	NR
16	Hirota	1995	2	19	46	0	0	mRS	NR	0.5–24
17	Horowitz	2006	4	10	19	0	0	mRS	0–6	0–6
18	Hosoda	1995	3	0	0	8	12	GOS	6	NR
19	Iijima	2005	3	65	72	0	0	mRS	3–6	3–27
20	Im	2009	3	46	0	0	0	mRS	NR	NR
21	Jartti	2010	3	0	38	0	0	GOS	1–34	NR
22	jin	2013	1	40	58	0	0	GOS	3–78	3–73
23	Kashiwagi	2000	5	0	0	35	0	GOS	1	NR
24	Khurseed	2008	2	0	0	13	99	GOS	6–60	NR
25	Kim	2011	4	70	0	0	0	mRS	3–6	6–24
26	Kim	2013	4	27	3	69	9	Death	0–6	0–6

27	Kocaeli	2011	3	0	0	0	29	GOS	6	NR
28	Kunert	2013	4	0	0	NR	NR	NR	> 36	>36
29	Kwon	2002	1	13	0	0	0	GOS	NR	NR
30	Lubicz*	2012	2	11	6	0	0	mRS	NR	6–60
31	Molyneux*	2005	5	0	162	0	139	mRS	2–12	2–12
32	Morgan*	2010	5	0	0	263	0	mRS	1.5	NR
33	Mortimer*	2014	4	53	241	0	0	GOS	3–6	3–17
34	Mori	2011	4	0	0	100	0	mRS	3	0
35	Nussbaum	2007	4	0	0	169	0	GOS	6	NR
36	Oishi	2009	2	44	58	0	0	GOS	TD	6–71
37	Penchet	2007	2	0	0	11	111	GOS	TD	NR
38	Prat	2007	3	0	0	0	12	GOS	12	NR
39	Quadros	2007	3	21	49	0	0	mRS	1–42	1–43
40	Regli	1999	3	2	0	28	0	GOS	TD	NR
41	Regli*	2002	4	1	0	35	0	GOS	12	NR
42	Rhee	2006	1	0	0	63	0	GOS	1	NR
43	Richling	2000	2	0	18	0	83	GOS	3–79	0–24
44	Rodriguez	2012	3	0	0	0	42	mRS	12	NR
45	Roy*	2001	1	14	0	0	0	mRS	NR	NR
46	Shimoda	1997	2	0	0	0	47	GOS	NR	NR
47	Suzuki	2009	3	67	48	0	0	mRS	3–108	0–24
48	Tenjin	2011	1	0	3	0	30	mRS	2	NR
49	Vendrell	2009	1	51	91	0	0	GOS	0–84	0–84
50	Yeon	2010	2	0	0	85	0	mRS	6	NR
51	Zhou	2012	3	13	16	0	0	mRS	1–48	1–21

*Assessed with the Cochrane Collaboration's risk of bias assessment tool for randomized trials (maximum 7 points).
†Numbers of patients with MCA aneurysms.
‡Data from a prospectively kept database.
FU, follow-up; GOS, Glasgow Outcome Scale; MCA, middle cerebral artery; mRS, Modified Rankin Scale; NOS Scale, Newcastle–Ottawa quality assessment scale for cohort studies (maximum 6 points); NR, not reported; TD, till discharge.

Table 2.2. Baseline characteristics of studies reporting on MCA aneurysms

	Unruptured		Ruptured	
	Coil	Clip	Coil	Clip
Studies (n)	25	19	25	15
Patients (n)	842	1332	1149	742
Aneurysms (n)	929	1480	1149	742

Study characteristics

All included studies, except one randomized controlled trial, were cohort studies. Ten studies were based on prospective data. The risk of bias in the cohort studies was high, with no study receiving the maximum of 6 points on the NOS Scale and seven studies receiving 1 point (Table 2.1).

Clinical outcome

Unruptured aneurysms

The follow-up period ranged from time to discharge to 108 months.

Favorable outcome was reported in 97.0% and 97.2% of cases after coiling and clipping, respectively. Death rate was 1.1% in patients treated by coiling and 0.3% in patients treated by clipping (Table 2.3). In the coiled group, this included one death caused by a myocardial infarction 3 months after treatment that was not likely caused by the treatment or hospital stay. Ischemia was the main cause of death in both groups (see Table S2.1 in supplementary appendix).

Ischemia was reported in 10.4% of cases after coiling and in 2.9% of cases after clipping. Post-treatment hemorrhages were reported in 3 of 495 patients (0.6%) after coiling and documented as negative in two clip studies including 152 patients. Clinical outcome after a post-treatment hemorrhage was favorable in one patient, unfavorable in one patient, and unknown in the other. Initial occlusion rates were unknown in these patients.

Ruptured aneurysms

The follow-up period ranged from time to discharge to 108 months.

Favorable outcome was reported in 77.1% of cases after coiling and in 72.8% after clipping. In the studies reporting on WFNS and HH on admission, 20.9% (168/802) of patients with coiled ruptured aneurysms and 35.3% (114/323) of patients with clipped ruptured aneurysms were in a poor initial neurological condition (WFNS/HH grade 4–5). Death rate was 8.4% and

Table 2.3. Clinical outcome reported for patients with MCA aneurysms

	Unruptured				Ruptured			
	Coil		Clip		Coil		Clip	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Total number of patients	842		1332		1149		742	
Favorable outcome	679/700	97.0 (95.5–98.1)	1132/1165	97.2 (96.0–98.0)	763/990	77.1 (74.5–79.7)	449/617	72.8 (69.3–76.3)
Death	9/842	1.1 (0.5–2.0)	4/1308	0.3 (0.1–0.8)	82/981	8.4 (6.7–10.3)	76/516	14.7 (11.7–17.8)
Intraprocedural rupture	13/549	2.4 (1.3–4.0)	NR	NR	30/544	5.5 (3.8–7.8)	NR	NR
Ischemia	45/432	10.4 (7.5–13.3)	27/924	2.9 (1.9–4.2)	46/350	13.1 (9.6–16.7)	42/251	16.7 (12.1–21.4)
Posttreatment hemorrhage	3/495	0.6 (0.1–1.8)	0/152*	0.0 (0.0–2.4)	10/618	1.6 (0.8–3.0)	7/157†	4.5 (1.8–9.0)

Favorable outcome mRS 0–2, GOS 4–5.
*Numbers based on data from two studies.
†Numbers based on data from five studies.
GOS, Glasgow Outcome Scale; mRS, modified Rankin Scale; n, number of events/patients; NR, not reported.

Table 2.4. Imaging outcome rates in coiled MCA aneurysms

	All aneurysms		Unruptured aneurysms		Ruptured aneurysms	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Total	2065*		929		1149	
Initial complete occlusion†	879/1568	56.1 (53.6–58.5)	191/355	53.8 (48.6–59.0)	296/455	65.1 (60.7–69.4)
Initial neck remnant†	520/1568	33.2 (30.8–35.5)	127/355	35.8 (30.8–40.8)	123/455	27.0 (23.0–31.1)
Initial incomplete/failed	168/1568	10.7 (9.2–12.2)	36/355	10.1 (7.0–13.3)	38/455	8.4 (6.0–11.3)
FU complete occlusion†	610/931	65.5 (62.5–68.6)	174/232	75.0 (69.4–80.6)	173/268	64.6 (58.8–70.3)
FU neck remnant†	214/931	23.0 (20.3–25.7)	40/232	17.2 (12.4–22.1)	78/268	29.1 (23.7–34.5)
FU incomplete	69/931	7.4 (5.8–9.3)	11/232	4.7 (2.4–8.3)	17/268	6.3 (3.7–10.0)
Retreatment	88/1286	6.8 (5.5–8.4)	22/346	6.4 (4.0–9.5)	16/175	9.1 (5.3–14.4)

Percentages based on number of aneurysms.
*Total number of aneurysms includes data from studies making no difference between unruptured and ruptured aneurysms.
†Both considered adequate occlusion.
FU, follow-up; n, number of aneurysms; NR, not reported.

14.7% in patients treated by coiling and clipping, respectively (Table 2.3). It was not possible to determine the exact cause of death in these patients. Ischemia was reported in 13.1% after coiling and in 16.7% after clipping. Post-treatment hemorrhages were reported in 10 (1.6%) of 618 patients after coiling. Clinical outcome was favorable in 3 of these 10 (30.0%) patients, unfavorable in 3 (30.0%) patients, and unknown in 4 (40.0%). In 4 (40.0%) of these 10 patients, there was a neck remnant after coiling, in 1 (10.0%) the initial occlusion rate was 100%, and in the remaining 5 (50.0%) the occlusion rate was unknown.

In five studies on clipped ruptured aneurysms, 7 (4.5%) of 157 patients had a post-treatment hemorrhage at follow-up. All other clip studies did not report on this. Clinical outcome was unfavorable in 6 (85.7%) of these 7 patients and unknown in 1 patient. The initial occlusion rates of these aneurysms were unknown.

Imaging outcome in all aneurysms

The follow-up period ranged from time to discharge to 84 months.

Initial adequate occlusion was achieved in 89.6% and 92.1% of cases after coiling of unruptured and ruptured aneurysms, respectively (Table 2.4). Only three studies on clipping (Choi et al., Diaz et al., and Kunert et al.) described 98.0%, 100%, and 96.2% adequate aneurysm occlusion, respectively, during follow-up with CT angiography or DSA.

Retreatments in all aneurysms

In 16 studies with 1286 patients with coiled aneurysms, 88 (6.8%) retreatments were reported (Table 2.4). No deaths were reported after retreatment of recanalized aneurysms. Clip studies did not report on retreatments.

Discussion

This review shows that favorable outcome rates are high, after both coiling and clipping of unruptured and ruptured MCA aneurysms, and that mortality is low. The data in this review should however be interpreted with care as the risk of bias was high for the majority of the studies.

There seems to be an advantage for clipping of unruptured aneurysms with respect to death rate. Favorable outcome rates after coiling and clipping of unruptured aneurysms were comparable to the 95.6% and 95.9% rates reported in the International Study of Unruptured Intracranial Aneurysms (ISUIA) study, whereas death rates for coiling and clipping were lower than the reported death rate for all aneurysm locations in the ISUIA study (3.4% for coiling and 2.7% for clipping, respectively).[15] The post-treatment hemorrhage rate after coiling of unruptured

aneurysms was comparable with that reported in the Unruptured Cerebral Aneurysm Study (UCAS) study, varying between 0.23% and 1.56% in unruptured MCA aneurysms of 3–9 mm,[16] but higher than the per year rupture rate of 0.1% in all untreated unruptured aneurysms <7 mm in the ISUIA study.

It is therefore unclear whether treatment of unruptured aneurysms has an advantage over a wait and see policy. A prospective randomized trial to determine the best strategy in unruptured aneurysms comparing coiling and clipping with conservative management seems warranted, although recent endeavors have proved unsuccessful.[17]

In this review it was not possible to separate periprocedural thromboembolic events from clinically apparent ischemia or ischemic changes reported on imaging studies. Although ischemia is reported more frequently after coiling than after clipping of unruptured aneurysms, this did not affect the favorable outcome rate, possibly because not all reported thromboembolic events led to clinical sequelae. The higher frequency of thromboembolic complications might be explained by an increased likelihood to detect thromboemboli events during the coiling procedure. Furthermore, follow-up MR imaging, including T2 weighted and three-dimensional time of flight MR angiography images, are more routinely performed after coiling to assess the occlusion rate of the coiled aneurysm, so ischemic changes are more readily detected.

In ruptured aneurysms, there seems to be an advantage of coiling with respect to clinical outcome rate and post-treatment hemorrhage rate. However, the lower death rate after coiling than after clipping is probably related to the fact that neurological status on admission was worse in the clipping group. The reason could be that patients with large intracranial hematomas carrying a worse prognosis are probably more often operated on for the purpose of decompression and/or hematoma evacuation, but we could not confirm this in our review as most studies did not report on this subject. An additional factor related to poor outcome could be that morphologically complex aneurysms are often unsuitable for coiling, and therefore more prone to be clipped, during often technically challenging procedures.

After coiling and clipping of ruptured aneurysms, the favorable outcome rates were comparable with the overall favorable outcome rates in the ISAT study (76.3% and 69.4%, respectively), suggesting that the risk profile and treatment of MCA aneurysms, which are subject to regular coil or clip treatment, does not differ from aneurysms in other locations.

The post-treatment hemorrhage rate in patients with coiled ruptured MCA aneurysms in this review seemed lower than the overall post-treatment hemorrhage rate within 1 year for ruptured aneurysms in the ISAT trial (2.6%) and the Cerebral Aneurysm Rerupture After Treatment (CARAT) study (3.4%) but this might be caused by the more variable time to follow-up.

The post-treatment hemorrhage rate in patients with clipped ruptured MCA aneurysms was higher than the overall rate for clipped ruptured aneurysms in the ISAT trial (1.0%) and the CARAT study (1.3%). The limitation in the 'coil' and 'clip' data is that not all studies commented on post-treatment hemorrhage. Assuming that the lack of complete reporting on this implies that there were no post-treatment hemorrhages, the percentages may be equal. Again, the lack of standardization in reporting on aneurysm repair hinders solid conclusions.

Intraprocedural aneurysm ruptures were only described in coil studies and were less frequent in unruptured than in ruptured aneurysms. None of the studies on clipping reported on intraoperative ruptures. During clipping, an intraoperative hemorrhage can usually be controlled effectively by temporary clipping of the afferent artery, in combination with removal of the extravasated blood. After stabilization, the aneurysm can be definitively occluded. Possible negative side effects of these hemorrhages are difficult to determine and are therefore probably not registered as a complication.

Follow-up imaging after coiling lacked a strict time interval, which makes calculations on short to mid term follow-up (< 1 year) difficult, if not impossible. However, the adequate occlusion rate was high initially and seemed stable during follow-up. This review also showed that follow-up imaging was not routinely performed after clipping. Even in a recently published review including single center, single surgeon data, follow-up imaging was performed in only 22% of patients.[18]

Limitations of this review are that most studies were retrospective and no study described the neurological condition before admission. This additional information can prove crucial when interpreting the final neurological condition during follow-up. Overall, there was a lack of standardization on reporting without a clear description of patient selection, clinical status on admission, morphological aspects and size of the aneurysms, follow-up period, clinical outcome, and a clear description of complications. For example, the reported clinical and imaging follow-up periods were highly variable. To improve comparison of future studies on aneurysm treatment, standard reporting should be instigated according to recently published guidelines, as this will allow for better comparison of coiling versus clipping of unruptured and ruptured aneurysms, with more solid conclusions on what is the best possible treatment modality.[19,20] Without these improvements, it will not be possible to draw definitive conclusions from a future systematic review on MCA aneurysm treatment.

Bias plays a major role in treatment selection. Local availability, skill set, and experience of the operator will mainly determine what treatment choice is made for the individual patient. In addition, financial incentives may bias treatment selection. Some advocate a rather rigid

clipping strategy for MCA aneurysms because morbidity and mortality are low, and it gives neurosurgeons the opportunity to maintain their clipping skills.[4] On the other hand, others treat MCA aneurysms solely endovascularly, including stent assisted coilings, with much higher complication rates.[5]

The best policy for the individual patient is probably to be treated in a large neurovascular center, with a high level of expertise in both coiling and clipping, that uses a multidisciplinary approach to customize the best possible treatment based on the individual patient's clinical condition and aneurysm morphology.

Conclusion

Both coiling and clipping are procedures with low mortality and morbidity rates, and although it may seem that coiling is preferable for ruptured MCA aneurysms and clipping for unruptured MCA aneurysms, no definitive conclusions can be drawn from this systematic review due to the variation in study design and lack of standardization in reporting on patients' clinical status and on the morphological aspects of the MCA aneurysms after treatment. Standardized observational studies from prospectively kept databases are needed to allow stronger conclusions to be made on what is the best treatment for MCA aneurysms.

Comparable with aneurysms in other locations, a multidisciplinary approach in large volume neurovascular centers is therefore recommended with selection of the optimal treatment modality based on the clinical condition of the patient and the morphological aspects of the aneurysm.

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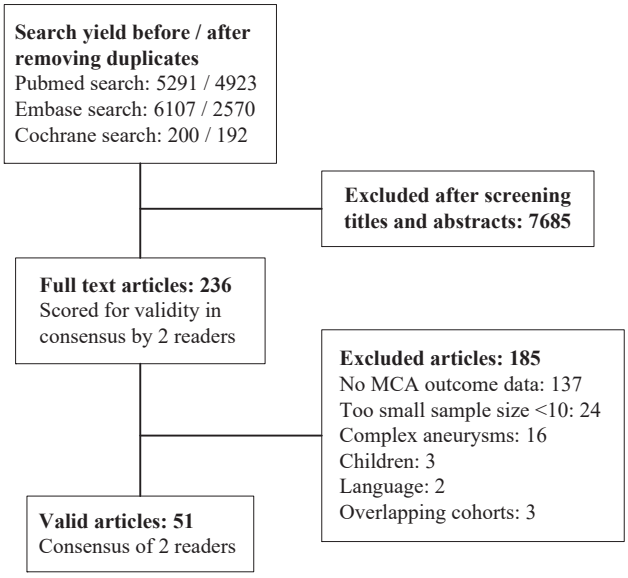
Appendix

Supplementary Table S2.1. Cause of death in patients with unruptured MCA aneurysms

Cause of death	Coil unruptured	Clip unruptured
Ischemia N (%)	2 (22.2)	2 (50.0)
Intraoperative rupture N (%)	1 (11.1)	
Posttreatment hemorrhage N (%)	2 (22.2)	
Myocardial infarction N (%)	1 (11.1)	
Bronchopneumonia N (%)	1 (11.1)	
ICA injury N (%)		1 (25.0)
Unknown N (%)	2 (22.2)	1 (25.0)
Total	9/ 842 (1.1%)	4/1308 (0.3%)

N, number; ICA, internal carotid artery.



Supplementary Figure S2.1. Flow diagram of literature search.

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3.

Ruptured middle cerebral artery aneurysms with a concomitant intraparenchymal hematoma: the role of hematoma volume

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Abstract

Purpose: To study whether clinical outcome data from our patient cohort could give support to the new recommendation in the AHA/ASA guidelines for the management of aneurysmal subarachnoid hemorrhage that states that microsurgical clipping may receive increased consideration in patients with ruptured middle cerebral artery (MCA) aneurysms and large (> 50 mL) intraparenchymal hematomas, while clinical outcome data supporting this recommendation are sparse.

Methods: We reviewed the clinical and radiological data of 81 consecutive patients with MCA aneurysms and concomitant hematomas admitted between January 2006 and December 2015. The relation between (semi-automatically quantified) hematoma volume (< or > 50 ml), neurological condition on admission (poor: GCS < 8 or non-reactive pupils), treatment strategies (no treatment, coiling, or clipping with or without decompression and/or clot removal), and outcome (favorable: mRS score 0–3) was evaluated.

Results: Clinical outcome data were available for 76 patients. A significant difference in favorable outcome (17 vs 68%) was seen when comparing patients with poor and good neurological condition on admission ($p < 0.01$). Patients with hematomas > 50 ml had similar outcomes for coiling and clipping, all underwent decompression. Patients with hematomas < 50 ml did not show differences in favorable outcome when comparing coiling and clipping with (33 and 31%) or without decompression (90 and 88%).

Conclusion: Poor neurological condition on admission, and not large intraparenchymal hematoma volume, was associated with poor clinical outcome. Therefore, even in patients with large hematomas, the neurological condition on admission and the aneurysm configuration seem to be equally important factors to determine the most appropriate treatment strategy.

Introduction

The prognosis of patients with ruptured middle cerebral artery (MCA) aneurysms is worse when the subarachnoid hemorrhage is complicated by an intraparenchymal hematoma, with a reported 6 months' mortality of 13–56%, even after aggressive treatment with decompression, clot removal, and clipping of the aneurysm.[1–3] Studies on clot removal and decompression after coiling of ruptured aneurysms report somewhat more promising results, with a 6 months' mortality of 20–30%, although these studies include aneurysms on all locations, including the MCA.[4–6]

A new recommendation in the guidelines for the management of aneurysmal subarachnoid hemorrhage of the American Heart Association states that microsurgical clipping may receive increased consideration in patients presenting with large (> 50 ml) intraparenchymal hematomas and middle cerebral artery aneurysms.[7] However, clinical outcome data supporting this recommendation are sparse and the reference that was used in this guideline does not clearly define hematoma volumes.[8] Other studies on patients with ruptured MCA aneurysms and intraparenchymal hematoma mostly focus on a subgroup of patients, such as patients with WFNS grades IV and V on admission, or on one of the several treatment strategies (coiling or clipping with or without clot removal and/or clot removal), due to which important information could be missing.[1–5,9]

For all patients admitted to our hospital with a ruptured MCA aneurysm and a concomitant intraparenchymal hematoma, we retrospectively evaluated the association between intraparenchymal hematoma volume, neurological condition on admission, and any combination of treatment options (no treatment, coiling or clipping, decompression, and clot removal) and clinical outcome.

Methods

Study design

This research was exempt from review by the local institutional ethical committee. The clinical charts and imaging studies (CT, MR, DSA) were reviewed of all consecutive patients with a CTA- or DSA-proven ruptured MCA aneurysm and a concomitant intraparenchymal hematoma admitted between January 2006 and December 2015 to our hospital, which acts as a tertiary referral center for patients with a SAH.

Demographic data, time of initial hemorrhage and hospital admission, Glasgow Coma Scale (GCS) score and WFNS score on admission, neurological findings, rebleeding, and the presence of an intraparenchymal hematoma were collected.[10,11] If a patient was transferred to our hospital under sedation, the last known GCS score was used. Poor neurological condition on admission was defined clinically as a GCS score < 8 and/or abnormal pupil reactions. In case the neurological condition changed during admission and before treatment, the last scores before treatment were used for calculations.

The treatment strategies were divided into three categories: no (endovascular or surgical) treatment, coiling, or clipping of the aneurysm. Coiling and clipping could be accompanied with decompression and clot removal. Decompression was defined as a hemicraniectomy on the side of the intraparenchymal hemorrhage without replacing the bone flap in the same procedure or as clot removal with or without replacing the bone flap in the same procedure. The decision to perform decompression with or without clot removal was at the neurosurgeons discretion. Clot removal was scored as having been performed in case it was specifically mentioned in the operative report. In patients treated with decompression and clipping of the aneurysm, we secondarily evaluated whether the aneurysm had been considered suitable for coiling or not. Indications for extraventricular drain (EVD) placement were hydrocephalus and comatose condition. The EVD strategy was 15–20 cm H_2O above Monro in patients with untreated aneurysms and 5–10 cm H_2O above Monro in patients with treated aneurysms. Mannitol was only given in case of intractable raised intracranial pressure.

The intraparenchymal hematoma volume (in ml) and the adjoining intra-Sylvian hematoma volume was delineated by an Bautomatic hematoma segmentation algorithm and corrected in consensus by two observers (IJZ and WS) on the baseline non-contrast CT-scan (5 mm slices) using ITK Snap version 3.4.0 (http://sourceforge.net/projects/itk-snap).[12] As it is very difficult to differentiate blood in the Sylvian fissure from true intra-Sylvian hematoma, we assessed the total hematoma volume. The calculated volume was then dichotomized into < or > 50 ml, conforming to the new AHA/ASA guidelines.[7]

The baseline CT-scan was used to assess hematoma side, hematoma location, midline shift, and hydrocephalus. A temporal lobe hematoma was defined as a hematoma located in the temporal lobe with or without secondary extension to the frontal or parietal lobe. Rebleeding was defined as an additional bleeding from the causative aneurysm after the initial bleeding, determined by an increase of blood on a plain head CT-scan, or by outflow of fresh blood from an external ventricular drain. In case of rebleeding before treatment, the blood volumes after rebleeding were used for analyses. In those patients who required decompression, the time interval between hospital admission and the start of surgery and decompression was measured.

Decompression within 6 hours of hospital admission was defined as urgent. If coiling was performed within this interval and prior to decompression, the delay between the coiling and the start of the decompression was also evaluated.

Complications (aneurysm rupture, procedure-related thromboemboli, possible procedure-related ischemia, and delayed cerebral ischemia (DCI)) were recorded. Procedure-related thromboembolic/ischemic events were defined as a visible thromboembolus on angiography during coiling or as permanent clipping of a vessel during surgery, or as new hypodensities in the treated vascular territory on a CT within 48 hours after an otherwise uncomplicated procedure. DCI was defined as any new focal neurological deficit (motor, sensory, or speech), or a decrease of two points or more on the GCS, that could not be attributed to other causes such as hydrocephalus, electrolyte or metabolic disturbances, rebleeding, or post-treatment complications or infections, and lasted for at least 1 hour.[13]

We evaluated the overall clinical outcome after 3 to 6 months using the modified Rankin scale (mRS).[14] Favorable outcome was defined as a mRS score of 0–3 in concordance with recent publications on the treatment of MCA aneurysms with associated hematomas.[1,15]

Statistical analysis

Continuous variables were presented as mean (SD) for normally distributed variables and as median (IQR) for non-normally distributed variables. Continuous variables were tested using the Shapiro-Wilk test ($W > 0.9$ is considered as a normally distributed variable). Categorical variables were presented as percentages. Categorical variables were tested using the Fisher's exact test. Values of $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics and treatment complications

Eighty-one consecutive patients with a ruptured MCA aneurysm were identified. Five patients were lost to follow-up after transfers to other hospitals (four to other countries). Baseline characteristics on admission and complications after treatment of the remaining 76 patients are presented in Table 3.1. No significant differences were found between coiling and clipping in the analysis of all the variables. An intraprocedural rupture occurred in six (8%) patients, five (83%) during clipping and one (17%) during coiling of the aneurysm. The thromboembolic/ischemic complications occurred in 17 patients (22%), in six (35%) patients during coiling of the aneurysm, and in 11 (65%) patients during or after clipping of the aneurysm. In four (67%)

Table 3.1. Baseline characteristics and treatment complications in 76 patients with a ruptured MCA aneurysm and a concomitant intraparenchymal hematoma

Demographic / clinical*	No treatment n (%)	Coiling n (%)	Clipping n (%)
Patients	11 (14)	28 (37)	37 (49)
Age in years (SD)	68 (11)	56 (14)	55 (11)
Female gender	8 (73)	23 (82)	26 (70)
Poor neurological condition on admission	9 (82)**	10 (36)**	16 (43)**
WFNS			
1	0	4 (14)	5 (14)
2	2 (18)	1 (4)	2 (5)
3	0	5 (18)	4 (11)
4	2 (18)	14 (50)	15 (41)
5	7 (64)	4 (14)	11 (30)
Radiological *			
Left-side hematoma	10 (91)	14 (50)	11 (30)
Temporal lobe hematoma***	8 (73)	21 (75)	31 (84)
Mean hematoma volume ml (SD)	30 (26)	29 (20)	27 (21)
Mean large (> 50 ml) hematoma volume ml (SD)	65 (10)	58 (13)	68 (13)
Midline shift > 2 mm	11 (100)	23 (82)	35 (95)
Intraventricular hematoma	9 (82)	13 (46)	25 (68)
Hydrocephalus	4 (36)	8 (29)	13 (35)
Complications*			
Intraprocedural rupture	0	1 (4)	5 (14)
Thromboembolie/ ischemia†	0	6 (21)	11 (30)
Delayed cerebral ischemia	1 (9)	7 (25)	10 (27)

*No statistical significant differences were found between all analyzed variables.
**Data missing in one patient.
***All other hematomas were located in the frontal lobe.
†(possible) procedure-related ischemia.

of six patients, Reopro (5 or 10 mg) was given during the coiling procedure. In four patients, a decompression was performed after coiling of the aneurysm, in all cases because of the ischemic complication. In four (36%) out of 11 patients treated with clipping, the ischemia could be directly related to the clipping procedure. In the other seven (64%) cases, new hypodensities were seen on the CT made < 48 h after an otherwise uncomplicated procedure. In nine (81%) out of 11 patients with ischemic complications, decompression was performed after clipping of the aneurysm, because of the intraprocedural complication or because of postprocedural neurological deterioration.

Treatment strategies and clinical outcome

The clinical outcome after 3–6 months' follow-up in relation to treatment strategy is presented in Table 3.2. Of the 11 (14%) patients who received no treatment, 10 patients had absent brain stem reflexes and subsequently died in hospital. One patient was not treated because of old age (89 years); she was living independently (mRS score 2) in a nursery home 6 months after discharge.

Overall, there was no significant difference in favorable outcome or 6 months' mortality between patients treated with coiling or clipping. Of the 65 treated patients, 19 (29%) died: five (18%) after coiling and 14 (38%) after clipping. Patients whose treatment included decompression showed a significantly worse favorable outcome compared to patients who were treated without decompression, and this was seen for both clipping and coiling ($p < 0.01$).

Urgent decompression was accomplished faster in a strict surgical approach. The mean (SD) (min-max) time interval between hospital admission and the start of the urgent surgical decompression was 161 (102) minutes (34–331). The mean (SD) (min-max) time interval between hospital admission and the start of the urgent surgical decompression after coiling was 268 (53) minutes (205–331).

Table 3.2. Clinical outcome after 3–6 months' follow-up in relation to treatment strategy in 76 patients with a ruptured MCA aneurysm and an associated intraparenchymal hematoma

		Clinical outcome n (%)		
Treatment strategy	Total group n (%)	mRS 0–3	mRS 4–5	mRS 6
	76	32 (40)	15 (19)	29 (38)
No treatment	11 (14)	1 (9)	0	10 (91)
Coiling	28 (37)	15 (54)	8 (29)	5 (18)
No decompression	10 (13)	9 (90)*	1 (10)	0
Decompression	9 (12)	2 (22)*	4 (44)	3 (33)
+ clot removal	9 (12)	4 (44)	3 (33)	2 (22)
Decompression < 6 hours	6 (8)	2 (33)	3 (50)	1 (17)
Clipping	37 (49)	16 (43)	7 (19)	14 (38)
No decompression	8 (11)	7 (88)*	0	1 (13)
Decompression	9 (12)	2 (22)*	2 (22)	5 (56)
+ clot removal	20 (26)	7 (35)	5 (25)	8 (40)
Decompression < 6 hours	15 (20)	3 (20)	5 (33)	7 (47)

mRS, modified Rankin scale.
*Significant difference in favorable outcome between no decompression and decompression ($P < 0.01$).

Hematoma volume

Clinical outcome after 3–6 months' follow-up in relation to treatment strategies and blood volumes < 50 or > 50 ml is presented in Table 3.3. Overall, no significant differences in favorable outcome were seen when comparing patients with a hematoma volume > 50 ml (29%) or < 50 ml (45%).

All treated patients with a hematoma volume > 50 ml were treated with decompression (with or without clot removal). No significant difference in clinical outcome was seen between coiling and clipping (with or without decompression and/or clot removal) in patients with a hematoma volume of > 50 ml. Although the mortality rate in patients with a hematoma volume < 50 ml was higher after clipping (38%) than after coiling (14%), this difference was not significant.

Clinical DCI occurred in two (14%) patients with a hematoma volume of > 50 ml and in 16 (26%) patients with a hematoma volume of < 50 ml, this difference was not significant.

Table 3.3. Clinical outcome after 3–6 months' follow-up in relation to treatment strategies and blood volumes > or < 50 ml in 76 patients with a ruptured MCA aneurysm and an associated intraparenchymal hematoma

	> 50 ml, n (%)				≤ 50 ml, n (%)			
		Clinical outcome				Clinical outcome		
	Total	mRS 0–3	mRS 4–5	mRS 6	Total	mRS 0–3	mRS 4–5	mRS 6
	14 (18)	4 (29)	3 (21)	7 (50)	62 (82)	28 (45)	12 (19)	22 (35)
No treatment	3(21)	0	0	3 (100)	8 (13)	1 (13)	0	7 (88)
Coiling	6 (43)	2 (33)	2 (33)	2 (33)	22 (35)	13 (59)	6 (27)	3 (14)
No decompression	0	0	0	0	10 (45)	9 (90)	1 (10)	0
Decompression*	6 (100)	2 (33)	2 (33)	2 (33)	12 (55)	4 (33)	5 (42)	3 (25)
Clipping	5 (36)	2 (40)	1 (20)	2 (40)	32 (52)	14 (44)	6 (19)	12 (38)
No decompression	0	0	0	0	8 (25)	7 (88)	0	1 (13)
Decompression*	5 (100)	2 (40)	1 (20)	2 (40)	24 (75)	7 (29)	6 (25)	11 (46)

No statistical significant differences were found between all analyzed variables.
mRS, modified Rankin scale.
*With or without clot removal.

Neurological condition on admission

Data on pupil reactions on admission were missing in three patients with a GCS > 8. The results of the remaining 73 patients are presented in Table 3.4.

Table 3.4. Clinical outcome after 3–6 months' follow-up in relation to treatment strategies and neurological condition before treatment in 73 patients with a ruptured MCA aneurysm and an intraparenchymal hematoma

	Poor neurological condition, n (%)				Good neurological condition, n (%)			
		Clinical outcome				Clinical outcome		
	Total	mRS 0–3	mRS 4–5	mRS 6	Total	mRS 0–3	mRS 4–5	mRS 6
	35 (48)	6 (17)**	8 (23)	21 (60)	38 (52)	26 (68)**	7 (18)	5 (13)
No treatment	9 (26)	0	0	9 (100)	1 (3)	1 (100)	0	0
Coiling	10 (29)	1 (10)	5 (50)	4 (40)	17 (45)	14 (82)	3 (18)	0
No decompression	0	0	0	0	10 (59)	9 (90)	1 (10)	0
Decompression†	10 (100)	1 (10)	5 (50)	4 (40)	7 (41)	5 (71)	2 (29)	0
Clipping	16 (46)	5 (31)	3 (19)	8 (50)	20 (53)	11 (55)	4 (20)	5 (25)
No decompression	2 (13)	2 (25)	0	0	6 (30)	5 (83)	0	1 (17)
Decompression†	14 (87)	3 (21)	3 (21)	8 (57)	14 (70)	6 (43)	4 (29)	4 (29)

Data on pupil reactions on admission missing in three patients.
mRS, modified Rankin scale.
**Significant difference (P < 0.01), also when only treated patients are analyzed (P < 0.01).
† With or without clot removal.

A significant difference in favorable outcome was seen when comparing patients with poor (17%) and good (68%) neurological condition on admission (p < 0.01). The difference (24 vs 66%) remained significant (p < 0.01) when only treated patients were analyzed.

Clinical DCI occurred in five (14%) patients with poor neurological condition and in 11 (29%) patients with good neurological condition on admission, this difference was not significant.

No significant difference in favorable outcome was seen in patients with poor or good neurological condition on admission who were treated with coiling or clipping, with or without decompression. There also was no significant difference in mortality rate in these patients.

All five patients with good neurological condition on admission who died after clipping of the aneurysm suffered from DCI.

Hematoma volume and neurological condition on admission

When the combination of neurological condition and intraparenchymal hematoma volume on admission were related to clinical outcome, neurological condition on admission (poor vs good) was more discriminative in determining clinical outcome than intraparenchymal hematoma volume (< or > 50 ml) (Figure 3.1). In the good grade patients with small hematomas, 16 (48%)

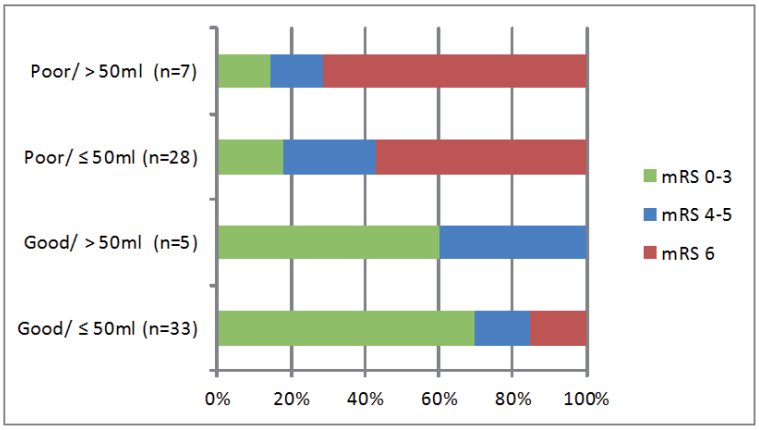

Figure 3.1. Neurological condition and hematoma volume in relation to clinical outcome after 3–6 months' follow-up in 73* patients with a ruptured MCA aneurysm and an associated intraparenchymal hematoma. *Data missing in three patients. No significant differences were found in the analysis of all the variables. mRS, modified Rankin Scale.

out of 33 patients were treated with decompression, four (25%) after coiling and 12 (75%) after clipping. In ten (30%) out of these 33 patients, a hemicraniectomy without replacing the bone flap was performed, in seven (70%) patients after clipping and in three (30%) after coiling, all due to complications/neurological deterioration during or after the procedure. In the other six patients, clot removal was performed during or after the aneurysm treatment. Favorable outcome was reached in 12 (86%) out of 14 patients after coiling, in 10 (56%) out of 18 patients after clipping, and in one (100%) untreated patient. The difference between coiling and clipping was not significant. Three out of five (60%) patients with a hematoma volume > 50 ml and a good neurological condition on admission had favorable clinical outcome, two after coiling and one after clipping with decompression and clot removal.

Discussion

In patients with a ruptured MCA aneurysm and a concomitant intraparenchymal hematoma, neurological condition on admission was strongly related with clinical outcome, whereas hematoma volume was not. Moreover, many patients with a poor neurological condition on admission had a hematoma volume < 50 ml. No significant difference in clinical outcome between coiling and clipping was found in patients with hematoma volumes of > or < 50 ml.

The 2012 American Heart Association guidelines for the management of aneurysmal subarachnoid hemorrhage states that microsurgical clipping may receive increased consideration

in patients presenting with large (> 50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms.[7] However, the reference that was used in this guideline does not clearly define hematoma volumes.[8] In our study, we observed that all patients with a hematoma volume of > 50 ml were treated with decompression, irrespective from neurological condition on admission. Simultaneously, all but two patients with poor neurological condition on admission were treated with decompression. While the number of patients presenting with a hematoma volume > 50 ml was quite low in comparison with those presenting in a poor neurological condition, this limits the numerical importance of volume, as compared to neurological condition to determine the need for decompressive surgery. Clinical outcome was worse after decompression also in patients with hematomas < 50 ml, who were in good neurological condition before treatment, because in these patients, decompression was often performed after complications or neurological deterioration during or after the coiling or clipping procedure. The higher complication rate after clipping might be explained by the coil-first policy in our hospital leaving the most challenging aneurysms for surgical treatment. Furthermore, a considerable proportion (4/11) of patients underwent an emergency operation for impending cerebral herniation, precluding any coiling procedure. Additionally, it is difficult to differentiate between edema, normal parenchymal changes after hematoma removal, and infarcts on a post procedural CT. Therefore, we might have overrated the clipping related ischemia. We suggest to perform a perfusion CT after these procedures to overcome this problem in future research. The higher hematoma decompression rate during clipping can be explained by the fact that the surgeon almost automatically comes across the hematoma when opening the dura.

Decompression can be preceded by coiling of the aneurysm, but this strategy is strongly dependent on the aneurysm configuration. The rationale of coiling first, despite the delay to decompression, is to secure the aneurysm prior to decompressive surgery, with or without hematoma evacuation, diminishing the risk of intraoperative rupture of the aneurysm. With respect to coiling and clot removal in patients with ruptured aneurysms, there are studies reporting 25–60% favorable outcome rates after coiling, but these included aneurysms in all locations. There are no studies solely reporting on this treatment strategy in patients with ruptured MCA aneurysms.[4–6]

When coiling is not possible, or when, based on neurological condition on admission, fast decompressive surgery is considered more important than primarily securing of the aneurysm, surgery is the preferred initial treatment. When we compare our outcome results with published data on surgical treatment of ruptured MCA aneurysms with a concomitant intraparenchymal hematoma (clipping in any combination with decompression and clot removal), one large study (144 patients) reported a higher overall mortality of 49%.[2] Several smaller studies reported lower mortality rates (13–29%) with favorable outcome rates ranging from 26 to 54%.[3,6,9]

Patient selection may explain these differences. One study, in Hunt & Hess III-V patients and a hematoma volume > 30 ml, reported a mortality rate of 25–30%, but also included aneurysms on other locations.[6] In another study, of 24 Hunt & Hess grade II-V patients, a similar (29%) mortality rate was found.[9] None of these studies divided the hematomas in >/< 50 ml.

We chose mRS 0–3 as favorable outcome according to recent literature on treatment of ruptured MCA aneurysms with a concomitant hematoma.[1,15] An additional argument is that the vast majority of the patients with a ruptured MCA aneurysm and a concomitant hematoma are admitted with a poor WFNS score of four or five, in our study 70% of the patients. The fact that patients are in a poor clinical condition on admission after a serious and life-threatening event, automatically leads to low expectations for a good outcome, not only with the doctors, but especially so with the patient and his or her family.

A limitation of our study is its retrospective nature, leading to missing data. Due to missing data the time from SAH ictus to decompression could not be analyzed, nor the occurrence of seizures. As of January 2011, a prospective database is maintained to minimize such data drop-outs. Furthermore, the sample size of our study is small, and therefore, the results have to be interpreted with some caution. The number of patients was not sufficient to perform a multivariate statistical analysis to detect possible confounding factors and to evaluate the association between both neurological status on admission and hematoma volume with clinical outcome due to which we had to analyze these factors as independent factors in a group comparison. Strength of our study is that we describe a consecutive patient cohort that was admitted over a period of 10 years' time in a tertiary center using a multidisciplinary approach for each individual patient. Also there are very little other studies describing such a cohort of patients with ruptured middle cerebral artery aneurysms and a concomitant hematoma. Another strength is the very precise hematoma volume measurement. The hematoma volumes in our study are much lower than those reported elsewhere.[1,16] For instance, the mean (SD) hematoma volume in the study by Stapleton et al. was 100 + 77 ml, while in our study, the mean (SD) hematoma volume (> 50 ml) was 68 + 15 ml and no patient had a hematoma volume of > 100 ml.[15] The difference can be explained by the method of volume measurement. In most studies, this is done with the ABC/2 method. Both are known to overrate the hematoma volume and small errors in measurement can lead to a high variation in volume.[17] Even though hematoma volume has no strong relation with outcome, we do propose a more standardized way to measure the hematoma volume to allow for better comparison of future studies. One such method to assess the total volume of subarachnoid hemorrhage has recently been published and shows a high degree of reproducibility.[12] This might lead to an improved prediction model, in which the total amount of blood in the different compartments (subarachnoid, parenchymal, and intraventricular) can be added. The clinical relevance is supported by a study reporting that

Sylvian hematomas without an intraparenchymal component can predict a favorable outcome in poor-grade aneurysmal SAH patients.[15] The high mortality rate in our study in clipped patients with a GCS > 8 and a hematoma volume < 50 ml was related to the occurrence of DCI and might be related to the distribution of blood between the subarachnoid and parenchymal compartments. This is in accordance with data from an earlier study in which a negative association of the existence of an intraparenchymal hematoma was seen in relation to the occurrence of clinical DCI.[18] The absence of clinical DCI in the patients with poor neurological condition on admission and a hematoma volume > 50 ml group can be explained by the poor outcome rate, as most patients either died within 3 days, or were in a too bad condition to discover clinical signs of DCI.

According to our results, neurological condition on admission together with the aneurysm configuration seems to be more important than hematoma volume to determine the best possible treatment strategy. The problem to study this specific patient group with ruptured aneurysms with concomitant hematomas is the large diversity in approach and experience which severely limits the design of a multicenter prospective trial. We therefore are limited to observational studies. However, we can improve on these studies by standardized registration of patients in prospective databases.

Summary

In patients with a ruptured middle cerebral artery aneurysm and a concomitant intraparenchymal hematoma, neurological condition on admission, and not large hematoma volume was associated with poor clinical outcome. The decision to perform decompressive surgery should be based more on neurological condition than on hematoma volume, especially after coiling of the aneurysm. Whether the decompression is combined with coiling or clipping of the aneurysm can be decided by the local neurovascular team based on the aneurysm configuration and the local expertise.

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4.

Automatic quantification of subarachnoid hemorrhage on noncontrast CT

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Abstract

Background and purpose: Quantification of blood after SAH on initial NCCT is an important radiologic measure to predict patient outcome and guide treatment decisions. In current scales, hemorrhage volume and density are not accounted for. The purpose of this study was to develop and validate a fully automatic method for SAH volume and density quantification.

Materials and methods: The automatic method is based on a relative density increase due to the presence of blood from different brain structures in NCCT. The method incorporates density variation due to partial volume effect, beam-hardening, and patient-specific characteristics. For validation, automatic volume and density measurements were compared with manual delineation on NCCT images of 30 patients by 2 radiologists. The agreement with the manual reference was compared with interobserver agreement by using the intraclass correlation coefficient and Bland-Altman analysis for volume and density.

Results: The automatic measurement successfully segmented the hemorrhage of all 30 patients and showed high correlation with the manual reference standard for hemorrhage volume (intraclass correlation coefficient = 0.98 [95% CI, 0.96–0.99]) and hemorrhage density (intraclass correlation coefficient = 0.80 [95% CI, 0.62–0.90]) compared with intraclass correlation coefficient = 0.97 (95% CI, 0.77–0.99) and 0.98 (95% CI, 0.89–0.99) for manual interobserver agreement. Mean SAH volume and density were, respectively, 39.3 ± 31.5 mL and 62.2 ± 5.9 Hounsfield units for automatic measurement versus 39.7 ± 32.8 mL and 61.4 ± 7.3 Hounsfield units for manual measurement. The accuracy of the automatic method was excellent, with limits of agreement of -12.9–12.1 mL and -7.6–9.2 Hounsfield units.

Conclusions: The automatic volume and density quantification is very accurate compared with manual assessment. As such, it has the potential to provide important determinants in clinical practice and research.

Introduction

Despite improvements, the treatment of SAH is associated with high fatality rates and affects fairly young adults: up to half of all cases of SAH are fatal within 30 days, and the mean age of presentation is 55 years.[1-5] There is strong agreement among studies that the amount of subarachnoid blood on initial NCCT has a highly predictive value regarding patient outcome and the incidence of vasospasm and concomitant delayed cerebral ischemia.[3,4,6-9] Hemorrhagic density may be of equal importance in predicting patient outcome, but this has not been validated properly.[3,10-12] Currently several grading systems are used to assess the initial clinical and radiologic features of SAH.[7,8,13-15] However, there is still an ongoing discussion about the optimal method of grading SAH on NCCT.[3,7,16-18] The 2 most commonly used scales of Fisher et al.[7] and Hijdra et al.[8] have come under criticism; authors referred to these scales as rather gross estimators, difficult to apply, lacking quantification, and cumbersome in the clinical setting.[3,17,19-22] Moreover, hemorrhage density is not considered in these scales. A quantitative volume and density measurement may reduce interobserver variability in comparison with current scales and would provide physicians with a potentially valuable tool for outcome prediction and treatment guidance.[23] As such, the aim of this study was to design and validate a reliable and easy-to-apply automatic measurement for subarachnoid hemorrhage quantification.

Materials and methods

Patient selection

This study is a substudy of a larger project evaluating the outcome of patients with ruptured middle cerebral artery aneurysms. NCCT image data of 50 consecutive patients with ruptured MCA aneurysms who were admitted to the Academic Medical Center hospital from January 2003 to March 2011 were retrospectively enrolled in this study. A subset of 20 consecutive patients was selected to form a training set for optimization of our method. The remaining 30 patients were used for validation. The inclusion criteria were the following: clinical diagnosis of SAH, available NCCT obtained within 72 hours after initial hemorrhage, and 18 years of age or older. Patients with previous aneurysm treatment by clipping or coiling, craniectomy, or craniotomy were excluded. A summary of the patient clinical and radiographic information is presented in Table 4.1. Informed consent was waived by the medical ethics committee.

Table 4.1. Clinical and radiographic characteristics of the study population

Characteristics	Test set (No.) (%)	Training set (No.) (%)
Sex		
Male	12 (40)	5 (75)
Female	18 (60)	15 (25)
Age (yr)		
45 or younger	7 (23)	5 (25)
46–60	16 (53)	11 (55)
Older than 60	7 (23)	4 (20)
IVH		
Yes	16 (53)	4 (20)
No	14 (47)	16 (80)
ICH		
Yes	19 (63)	12 (60)
No	11 (37)	8 (40)
MCA location		
Left	14 (47)	18 (10)
Right	16 (53)	2 (90)
WFNS at admission		
Grade I	11 (37)	9 (45)
Grade II	2 (7)	2 (10)
Grade III	2 (7)	4 (20)
Grade IV	8 (27)	3 (15)
Grade V	7 (23)	2 (10)
History of hypertension		
Yes	3 (10)	7 (35)
No	22 (73)	13 (65)
Aneurysm size		
< 5 mm	9 (30)	6 (30)
6–10 mm	14 (47)	12 (60)
11–15 mm	3 (10)	2 (10)
> 15 mm	3 (10)	–
Signs of DCI		
No	21 (70)	19 (95)
Yes	9 (30)	1 (5)
Paresis	1 (3)	1 (5)
Decreased consciousness	4 (13)	–
Hemiparesis and aphasia	3 (10)	–
Vasospasm	1 (3)	–

IVH indicates intraventricular hemorrhage; ICH, intracerebral hemorrhage; DCI, delayed cerebral ischemia; WFNS, World Federation of Neurosurgical Societies.

Imaging protocol

Whole-brain NCCT was performed on a Sensation 64 scanner (Siemens, Erlangen, Germany) and a Sensation 4 scanner (Siemens) with the following parameters: 120 kV, 380 mAs, reconstruction kernel = H40s, and 5-mm section thickness, resulting in volumes with 23–34 sections. The image data were anonymized.

Overview

Our proposed method for detection and quantification of blood after SAH is based on a relative density increase in NCCT images due to the presence of blood. The process started with an atlas-based segmentation to classify different brain structures, followed by a compensation for partial volume effect in the vicinity of the skull. Hereafter, evaluation of density was assessed to set a tissue-specific threshold for density-based segmentation of blood. A region-growing algorithm included subtle attenuated parts of the hemorrhagic areas.

Atlas-based segmentation

Atlas-based segmentation requires a reference image with a corresponding atlas, which classifies structures in this image. An experienced neuroradiologist (C.B.M.) selected an NCCT image of a healthy subject as a reference image, ensuring that no pathologies or image artifacts were present. Because the proposed hemorrhage detection method is based on a relative density increase in NCCT images, brain structures with different densities on NCCT images should be recognized. As such, brain tissue was labeled as the following: 1) GM, 2) WM, and 3) CSF.

The Laboratory of Neuro Imaging Probabilistic Brain Atlas (LPBA40)[24] was used for the labeling. The LPBA40 dataset provides the following: 1) average-intensity skull-stripped T1-weighted MR brain image; 2) probabilistic MR imaging tissue maps of WM, GM, and CSF; and 3) probabilistic maps for 56 delineated structures in the brain. The LPBA40 Atlas was registered with the reference image to produce the CT-based atlas.

Skull-stripping

Because the LPBA40 images are without skull, skull stripping of the NCCT reference image was required before registration. The skull-stripping started with thresholding to select and exclude the skull by using an established threshold of 100 Hounsfield units (HU). This threshold assured that calcifications were excluded and any hemorrhage was included.[25,26] After a 2D erosion with a disk-structuring element in each section, the remaining structures were detected by using 2D-connected component analysis. To discriminate brain tissue from other

soft tissues, we excluded connected components with small areas. When multiple connected components were present in a section, the component with its centroid closest to the centroid of the superior section was selected as brain tissue. Here we assume that superior sections only contain a single connected component because of the absence of soft tissues other than brain in the cranial part of the head. After selection of brain tissue, we performed a morphologic closing and dilation, resulting in the final brain mask.

Generation of a CT-registered atlas

All registrations were performed by using the open-source software Elastix (Version 4.6; http://elastix.isi.uu.nl).[27] First, the average-density LPBA40 MR brain image was registered to align with the skull-stripped reference image. Because multimodal images needed to align, mutual information was set as a similarity measure for registration. Registration was performed by a rigid and affine transformation first to correct for major differences in position, orientation, and size. Subsequently, a nonrigid B-spline registration was applied to correct for remaining differences in brain shape, and the result was inspected by a trained observer (A.M.B). Using the transformation from this registration, we transformed the anatomically labeled maps of the LBPA40 data with the use of Transformix (Version 4.6; http://elastix.isi.uu.nl)[27] to align with the reference CT image, resulting in the CT-registered atlas images used in the remainder.

Atlas-based segmentation of patient images

The CT-based atlas was used to label different brain tissue types in all patient images. By registration of the reference image with patient images, the CT-based atlas also aligned with patient data. Similar to the registration of the reference image with the LBPA40 atlas, this process was started with skull stripping. The regions of the patient images were classified by applying this transformation to the CT-based atlas. Because hemorrhages induce density changes, again, mutual information was set as a similarity measure in the registration to label patient NCCT images into GM, WM, and CSF.

Partial volume effect

The used image data with relatively thick sections of 5 mm had partial volume effects, resulting in higher density in the skull-brain transition zone. As a result, healthy tissue close to the skull may have density similar to that of blood. This makes it difficult separate images of true hemorrhage near the skull from artifacts, due to partial volume effects. There is however, a noticeable change in the width of the transition zone of healthy brain tissue and skull; this transition is wider in the presence of hemorrhage.

To differentiate hemorrhagic tissue from healthy tissue with partial volume effects, we estimated the density gradient at the transition of skull to healthy brain tissue, in which the gradient for hemorrhagic tissue is lower than that for healthy tissue with partial volume effects. This density gradient (v) is defined as the density difference (in Hounsfield units) between the skull and healthy brain tissue divided by the Euclidean distance between these points. The location of the points was found by selecting 2 positions on an orthogonal line over the transition of the brain and skull. The pixel closest to the brain tissue with a density of > 100 HU was selected as the first point (P_1), and the pixels closest to the skull with a density of < 50 HU, as a second point (P_2). The typical density gradients for partial volume effect and hemorrhagic brain tissue near the skull are illustrated in Figure 4.1. Using this separation, we excluded voxels with high densities and high gradients from further processing.

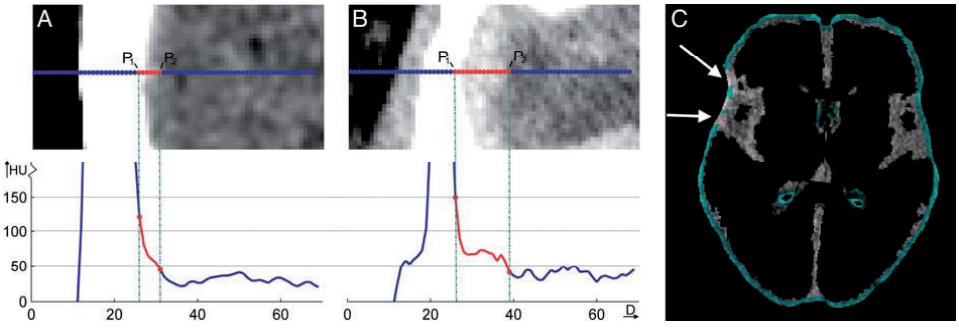

Figure 4.1. Illustration of differentiation between partial volume effect and hemorrhage in the vicinity of the skull. **A**, Calculation of the density gradient of an NCCT image with high hypodensities near the skull. High gradients are expected to be caused by partial volume effects in contrast to hemorrhages, which result in low gradients as seen in **B** and **C**. The pixels corresponding to low gradients (blue) are excluded from further segmentation. The white arrows mark the areas with high gradients present in the CSF image.

Correction for patient-specific density differences

Relative density differences of normal and hemorrhagic voxels can vary from patient to patient. These variations are mainly caused by partial volume effects in upper and lower sections and beam-hardening but may also be caused by differences in scanner type and brain tissue composition (old infarct, atrophy) and blood composition (age of hemorrhage, hematocrit). Because our method is based on relative density changes, this offset needed to be corrected, to come to an optimal threshold to discriminate blood from normal brain tissue. To estimate these small offsets, we divided recognized tissue types in each section into equal tiles in which the SD of the density was calculated. After visual inspection of an alternating number of tiles,

the optimal number of tiles was established (n = 64). Tiles with a small SD were expected to be free of blood. The densities in these tiles were used to estimate the mean density of that specific tissue type in that section. This process is illustrated in Figure 4.2. The "offset" was defined as the difference of the mean density of that tissue type and the values of the reference image. After correction for this offset, a first estimation of hemorrhage was defined as all voxels with a density higher than the adjusted threshold, which was defined by the mean density of the reference image per tissue type ± the SD.

In the interhemispheric fissure, the falx cerebri can be mistaken for blood and therefore requires additional analysis. The interhemispheric fissure was localized by using anatomic atlas regions adjacent to the midline. A blood-free segment of the falx was selected as the segment with a small SD of densities. K-means clustering was used to partition the area into 2 structures: normal brain tissue or the falx. Subsequently, the threshold to segment blood in the interhemispheric fissure was adjusted to the normal hyperattenuated falx.

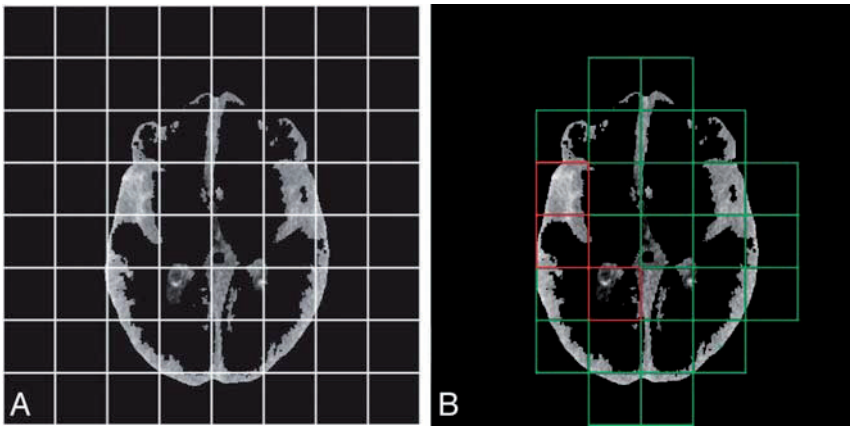

Figure 4.2. Illustration of the correction for patient-specific density differences. **A**, Each section of a specific tissue type (here CSF) is divided into 64 tiles, and the SDs of the density were calculated. **B**, Green tiles represent those with a low SD of the density and are expected to be free of a substantial amount of extravasated blood and therefore mainly consist of healthy brain tissue, whereas tiles with a high SD (red tiles) are more likely to contain hemorrhage. The densities in the green tiles were included in the calculation of the mean density of that tissue type. Comparison with the mean density of that tissue type in the reference image resulted in a density offset, which was corrected.

Region growing

The threshold, as described above, does not include subtle attenuated parts of the hemorrhage. To correct for this underestimation of blood volume, we used initial segmented hemorrhages as seeds for a region-growing algorithm. This algorithm examined all voxels in the vicinity of

the initial segmented hemorrhage to determine whether these voxels should be included in the segmentation. A voxel was included if the difference in its density and the average density of the segmented volume was smaller than a predefined threshold of mean density -1.5 times the SD.

Hemorrhage volume and density estimation

The volume of blood was determined as the multiplication of the segmented voxels by voxel size. For every segmented region of blood, there is a distribution of densities. Because the average density may be sensitive to small overestimations of the segmentation, which would include low-density voxels, the hemorrhage density was defined as the third quartile of the density distribution of the segmented volume.

Manual hemorrhage segmentation

The hemorrhage volume of 20 patients with SAH was selected for training and was manually delineated by radiologist I.A.Z. (with 8 years of experience) by using ITK-SNAP 2.4.0 (http://sourceforge. net/projects/itk-snap/files/itk-snap/2.4.0/).[28] The 30 hemorrhage volumes in the test set were delineated twice by radiologists I.A.Z. and R.v.d.B. (with > 15 years of experience) and were used for validation. Both observers were blinded to all clinical information and each other's results.

Fisher and Hijdra grading

Each patient was graded according to the Fisher and Hijdra scales by I.A.Z. and C.S.G. Both observers were blinded to all clinical data and reached a consensus. The sum score of the ventricles and cisterns was combined to obtain the final Hijdra score, ranging from 0 to 42.

Statistical analysis

The manual measurements of a single observer (I.A.Z.) were used as a reference standard to evaluate the accuracy of the automatic method. The difference in hemorrhage volume between the automatic and manual assessment and the interobserver variability of the manual hemorrhage segmentation was evaluated by a number of tests. At first, scatterplots were presented, and the interclass correlation coefficient (ICC) and its 95% CI with absolute agreement definition were calculated. The ICC was assessed according to the case 3 form of Shrout and Fleiss,[29] in which a 2-way ANOVA model is used for analysis. Additionally, a Bland-Altman analysis was performed to assess the bias and limits of agreement, in which the "bias" was defined as

the mean paired difference and limits of agreement.[30] Furthermore, the Dice coefficient[31] was calculated to determine the overlap of the volumes, and the ICC and its 95% CI of the hemorrhage density were assessed.

In addition, Fisher and Hijdra scale scores were compared with manual-delineated and automatic-determined volumes by constructing scatterplots and calculating, respectively, the Spearman rank correlation coefficient and the Pearson correlation coefficient and their 95% CIs.

Results

The test set included 30 patients, with a mean age of 55 ± 12 years, and 60% were women. The mean SAH volume was 39.71 ± 32.84 mL and 39.33 ± 31.49 mL, according to the manual and automatic methods, respectively. The ICC of the volume measurement between the automatic and manual measurements was 0.98 (95% CI, 96%–99%). The ICC of the volume-measurement interobserver agreement was 0.97 (95% CI, 77%–99%). Bland-Altman analysis indicated an average difference in SAH volume of -0.39 mL between the automatic and manual measurements, with limits of agreement ranging from -12.90 to 12.10 mL. For the 2 observers, the Bland-Altman analysis resulted in a bias of -6.22 mL, with limits of agreement ranging from -18.70 to 6.20 mL. The Dice coefficient of the manual and automatic measurements was 0.55 ± 0.24 and ranged from 0.00 to 0.83, in comparison with 0.64 ± 0.20 between the 2 observers.

The interobserver and accuracy measures are shown in Table 4.2 and Figure 4.3. The mean SAH density was 61.43 ± 7.26 HU and 62.23 ± 5.89 HU, according to the manual and automatic methods, respectively. The ICC of the hemorrhage density between the observers was 0.98 (95% CI, 89%–99%) and 0.80 (95% CI, 62%–90%) for the comparison of the manual reference and automatic method. In 1 case, observer 2 detected no hemorrhage; this case was excluded from the calculation of the manual interobserver variability regarding the density measurement only. Bland-Altman analysis indicated an average difference in SAH density of 0.80 HU between the automatic and manual measurements, with limits of agreement ranging from -7.58 to 9.18 HU. For the 2 observers, the Bland-Altman analysis resulted in a bias of 0.96 HU, with limits of agreement ranging from -1.52 to 3.44 HU.

The Fisher score was 2 in 3 patients (10%), 3 in 4 patients (13%), and 4 in 23 patients (77%). The Hijdra score ranged from 1 to 38, with a median and third quartile of 24 and 29, respectively. The correlation of the hemorrhage volume with the Fisher score and Hijdra score is shown in Figure 4.4. The Pearson correlation coefficient of the Hijdra score with manual volume measurement was 0.39 (95% CI, 0.04–0.63; $p < 0.05$), and with automatic measurement,

Table 4.2. Interobserver variability of manual SAH volume measurement and comparison of the manual and automatic methods

	ICC volume[a] (95% CI)	Bland-Altman volume limits of agreement (mL)	ICC density[a] (95% CI)	Bland-Altman density limits of agreement (HU)	Dice coefficient (mean and range)	No.[b]
Automatic interobserver	0.98 (0.96–0.99)	-12.90–12.13	0.80 (0.62–0.90)	-7.58–9.18	0.55 (0.00–0.83)	30
Manual interobserver	0.97 (0.77–0.99)	-18.68–6.24	0.98 (0.89–0.99)[c]	-1.52–3.44[c]	0.64 (0.00–0.86)	30

[a] Case 3 intraclass correlation coefficients using an absolute agreement definition.
[b] Number of NCCT scans included in the calculation.
[c] Number of NCCT scans included for calculation = 29.

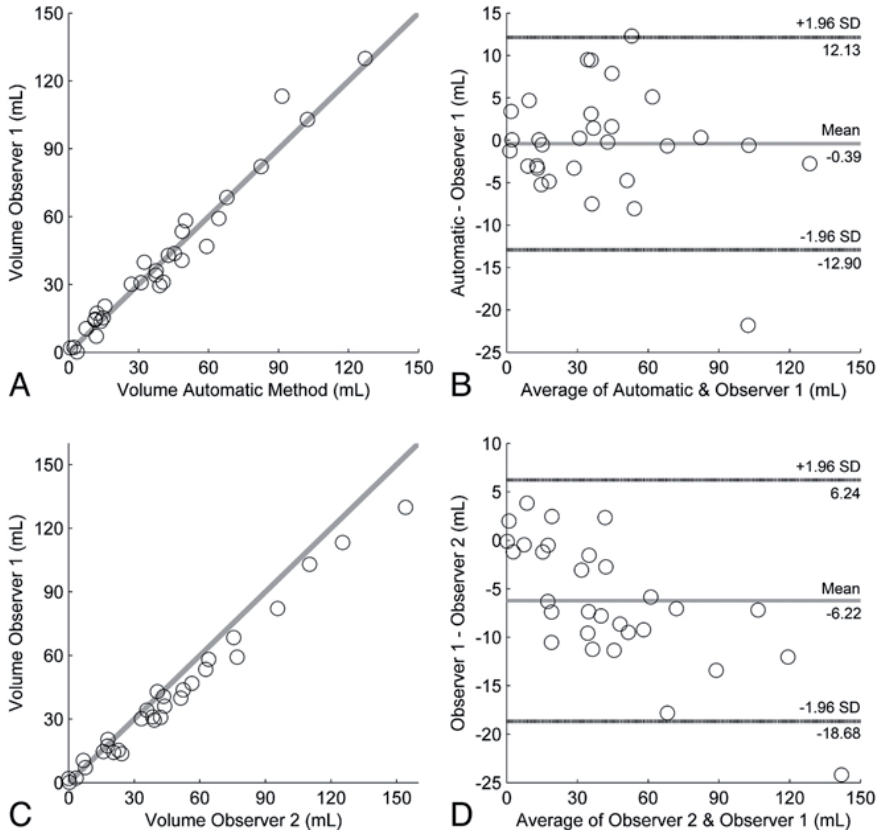

Figure 4.3. The accuracy of the volume measurement of the automatic method compared with that in observer 1. A, Accuracy depicted as a scatterplot. B, Accuracy shown by the Bland-Altman plot. Interobserver variability of the manual hemorrhage volume measurement depicted as C, scatterplot, and D, Bland-Altman analysis.

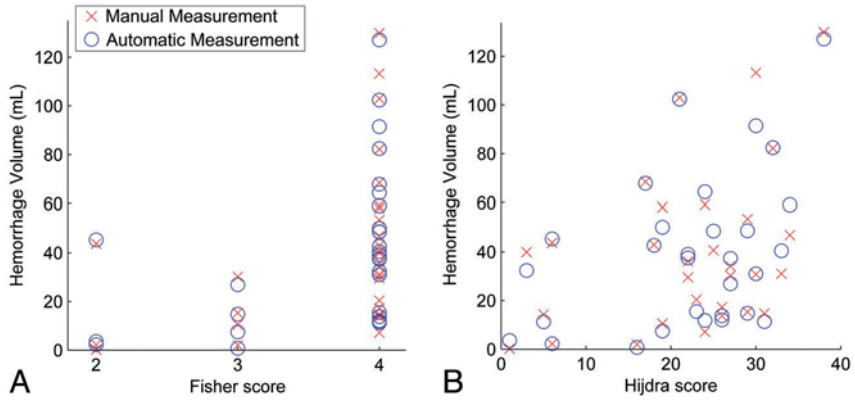

Figure 4.4. Correlation of the Hijdra score and Fisher score with hemorrhage volume after SAH assessed with scatterplots. A, The Fisher score with automatic volume measurement (blue) and manual volume measurement (red). B, The Hijdra score with automatic volume measurement (blue) and manual volume measurement (red).

0.42 (95% CI, 0.08–0.65; $p < 0.05$). The Spearman rank correlation coefficient of the Fisher score with a manual volume measurement was 0.49 (95% CI, 0.10–0.74; $p < 0.01$), and with automatic measurement, 0.50 (95% CI, 0.14–0.74; $p < 0.01$).

Discussion

In this study, we have presented a novel method for automatic hemorrhage volume and density quantification in NCCT scans of patients with SAH. Comparison with manual delineations in 30 patients with SAH with manual assessment showed an excellent agreement in blood volume and a good agreement in blood density.

Despite the general acceptance that the volume of blood after SAH provides information regarding prognostic outcome and guidance for treatment decisions, no method to estimate the real amount of blood so far has been successful. Sato et al.[23] proposed an automated measurement on 3D CT to quantify SAH on the basis of thresholding between 40 and 80 HU, which could rapidly measure SAH volume. However, the time needed to manually exclude the scalp and subcutaneous tissue was not taken into account. Furthermore, errors in volume of approximately 10 mL were unavoidable, partly because the volume was calculated by subtracting a mean value for tissues between 40 and 80 HU of healthy subjects from the patient image. Other computer-aided detection methods have been proposed for intracranial hemorrhages; however, these are not suitable to automatically quantify SAH. For instance, the method of Chan[32] is based on the symmetry of the ventricles, which are segmented by thresholding only.

Here, the assumption is made that no blood is present in the ventricles, which is often not the case in patients with SAH.

The Fisher scale has become the current historical standard for this purpose on NCCT. It was designed to predict cerebral vasospasm; however, its clinical utility has been questioned.[11,14,19,33] The Fisher scale is not comprehensive enough to serve as a primary grading system for SAH and to predict clinical outcome.[3] In this study, the Fisher scale fails to differentiate among hemorrhages with a small, moderate, or substantial amount of blood by categorizing grade 4 in 77% of the cases within a large range of 12–130 mL. Finding no blood on CT is rare, as is clot < 1 mm in true thickness, making grades 1 and 2 quite uncommon. The correlation of this scale with hemorrhage volume was moderate (0.49). Because there is strong agreement among studies that the amount of subarachnoid blood has highly predictive value regarding patient outcome, we believe that our proposed volumetric measurement has added value above the Fisher scale.[3,4,6-9] Moreover, Figure 4.4 illustrates the large range of hemorrhage volumes within single Fisher scales. Because of the low number of patients in Fisher grades 1 and 2, we could not perform any valuable statistical analysis.

Even though the method by Hijdra et al.[8] is more comprehensive than the Fisher scale, the correlation with the measurements of hemorrhage volume in this study was poor in comparison with our proposed method (0.39 versus 0.98). The Hijdra scale assigns grade 3 to a fissure or cistern when it is completely filled with blood, which does not indicate a certain volume. In addition, assessment of the Hijdra scale is a tedious task and may be impractical in an emergency setting.

Recently, Wilson et al.[34] proposed the Barrow Neurological Institute scale, a simple and quantitative method to grade the amount of blood and predict vasospasm. This scale categorized patients with SAH into 5 more evenly distributed classes than the Fisher scale and showed better interand intraobserver agreement. However, the clinical value has not been confirmed by other studies. Although this scale appears promising for the prediction of vasospasm, associations with SAH volume have not been reported. An example of the volume measurements is shown in Figure 4.5. The concordance of the automatic method with manual reference was excellent, despite a moderate Dice coefficient. This disagreement can partly be attributed to the tortuous shape of the cisterns. The observers perceived an image on the screen and delineated it by hand; this hand method results in smooth edges, whereas the automated method segments the image on a voxel-by-voxel basis, which results in ragged edges.

Another limitation for the current grading scales is that hemorrhage density, which may be equally important, is not considered.[3,10-12] This limitation addresses an additional advantage

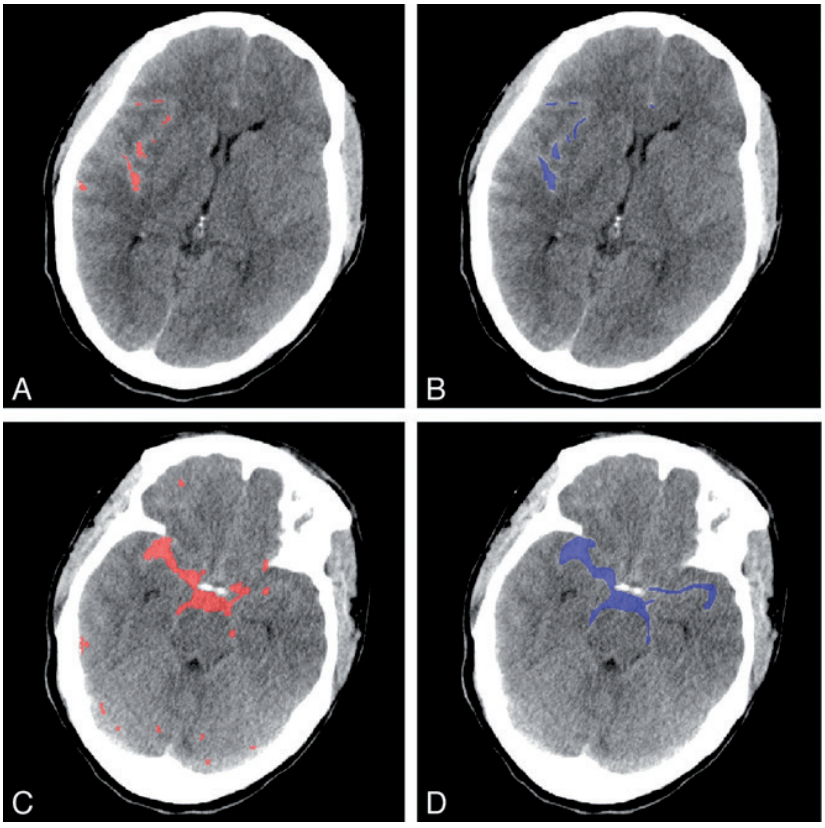

Figure 4.5. Example of the results of the automatic segmentation of extravasated blood after SAH and manual measurement. A, NCCT image, shown in red, with results of the automatic method of a relatively small hemorrhage. B, The same NCCT image and hemorrhage as delineated by observer 1 (blue). C, NCCT image with beam-hardening in an extreme degree. The automatic method, in red, shows deviations of the hemorrhage volume as delineated by observer 1 (D) in blue.

of the proposed automatic method, which reports a good ICC of the hemorrhage density measurement with the manual reference. This ICC was, however, approximately 18% lower than the interob server variability. Retrospective analysis showed that this difference was mainly caused by low agreement in patients with small hemorrhage volumes. When we included only SAH volumes > 5 mL (3 patients excluded), the ICC of the hemorrhage density of the automatic measurement and manual reference increased to (95% CI, 87%–98%). This increase can be partly explained by the difference in procedures regarding small hemorrhages; in the manual comparison, the observers delineated on the basis of personal experience and by using the contralateral hemisphere for comparison. Here, only slightly hyperattenuated blood could be detected, in contrast to the automatic method, which is threshold-based. No restrictions are to be expected regarding SAH quantification for such small hemorrhages.

In this study, the third quartile was chosen for the hemorrhage-density estimation. We believe that a measurement such as the mean is more sensitive to errors in the segmentation due to the difference in segmentation technique (voxel-by-voxel-based versus delineation by hand). The third quartile is, however, a heuristic approach.

SAH often is accompanied by intraventricular hemorrhage or intracerebral hemorrhage as seen in Table 4.1. The automatic method in this study was designed to include all blood present in the brain after SAH. Therefore, we believe this method has the potential to serve as a quantification measurement in other types of hemorrhagic strokes. As future work, it could be beneficial to differentiate among locations of hemorrhage to investigate the role of blood distribution in patients with SAH. This study was performed on image data of a population of patients who had SAH due to rupture of an MCA aneurysm. As a result, this study may be affected by a selection bias because these patients, especially, present with bleeding around the temporal and insular regions; however, in most patients, there was extension into the interhemispheric fissure and to the lower pontine cistern. All included NCCT images were obtained on 2 scanner types, with 1 reconstruction kernel. We do, however, expect no problems when using different scanner types because the automatic method corrects for these density differences.

The duration of manual segmentation was recorded for 19 patients only. The manual segmentation ranged between 5 and 23 minutes with a median of 15 minutes, which was considerably longer than the 2–5 minutes required for the Fisher and Hijdra grading. The automatic SAH assessment took an average of 5 minutes per patient on a modern computer. The computation times should be further reduced to make an approach as presented here available for clinical practice.

Furthermore, the automatic method may not recognize aneurysms and large vessels and categorizes them as part of the hemorrhage. Using the proposed method to quantify only the amount of extravasated blood may therefore lead to an overestimation of this volume. A solution for this issue could be to subtract a CTA from the NCCT image.

In this study, a method was designed to correct for partial volume and beam-hardening artifacts, which are more prominent in the anterior fossa near the skull base and in the posterior fossa. Despite these corrections, other CT artifacts, such as patient motion, may cause the automatic SAH quantification to fail. In addition, when beam-hardening is present in an extreme extent, the automatic segmentation may underestimate the hemorrhage volume because the artifacts are approached as a patient-specific density variation as seen in Figure 4.5. Furthermore, high-attenuated areas may be seen as hemorrhage. Although physics-based artifacts cannot be eliminated, techniques have been developed to correct for these quantitative and visual errors and could be beneficial for improvement of our method.[35,36]

Another point is that the threshold values used in the algorithm are dependent on the standard value in the images. Therefore, the method may be dependent on the image quality. Validation on different scanners and reconstruction techniques is therefore required.

We designed and validated our method to align the real hemorrhage volume and density after SAH. Evaluation with patient outcome is beyond the scope of this study because multiple factors other than radiographic evidence contribute to the prediction of patient outcome, including clinical scales such as those of Hunt and Hess[13] and the World Federation of Neurosurgical Societies.[3,15,37] A future study in which hemorrhage volume and density are combined with other factors is necessary to validate the full utility of this method as a predictor for patient outcome.

Conclusions

We have presented a fully automatic method for blood volume and density quantification in NCCT scans of patients with SAH. The automatic method showed an excellent accuracy and strong correlation with the manual reference standard. This approach is an easy-to-use (fully automatic) and observer-independent solution in assessing the volume and density and, as such, has the potential to assist in predicting patient outcome, guiding treatment decisions, and standardizing hemorrhage assessment across medical centers in multicenter studies.

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5.

Association of automatically quantified total blood volume after aneurysmal subarachnoid hemorrhage with delayed cerebral ischemia

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Abstract

Background and purpose: The total amount of extravasated blood after aneurysmal subarachnoid hemorrhage, assessed with semiquantitative methods such as the modified Fisher and Hijdra scales, is known to be a predictor of delayed cerebral ischemia. However, prediction rates of delayed cerebral ischemia are moderate, which may be caused by the rough and observer-dependent blood volume estimation used in the prediction models. We therefore assessed the association between automatically quantified total blood volume on NCCT and delayed cerebral ischemia.

Materials and methods: We retrospectively studied clinical and radiologic data of consecutive patients with aneurysmal SAH admitted to 2 academic hospitals between January 2009 and December 2011. Adjusted ORs with associated 95% confidence intervals were calculated for the association between automatically quantified total blood volume on NCCT and delayed cerebral ischemia (clinical, radiologic, and both). The calculations were also performed for the presence of an intraparenchymal hematoma and/or an intraventricular hematoma and clinical delayed cerebral ischemia.

Results: We included 333 patients. The adjusted OR of total blood volume for delayed cerebral ischemia (clinical, radiologic, and both) was 1.02 (95% CI, 1.01–1.03) per milliliter of blood. The adjusted OR for the presence of an intraparenchymal hematoma for clinical delayed cerebral ischemia was 0.47 (95% CI, 0.24 – 0.95) and of the presence of an intraventricular hematoma, 2.66 (95% CI, 1.37–5.17).

Conclusions: A higher total blood volume measured with our automated quantification method is significantly associated with delayed cerebral ischemia. The results of this study encourage the use of rater-independent quantification methods in future multicenter studies on delayed cerebral ischemia prevention and prediction.

Introduction

Delayed cerebral ischemia (DCI) occurs in 20%–30% of patients with aneurysmal subarachnoid hemorrhage (aSAH) and is associated with poor outcome.[1-3] Patients who develop DCI need costly intensive care. The cause of DCI is multifactorial, including larger and smaller vessel vasospasm, cortical spreading ischemia, microvascular dysfunction, and thrombosis.[3] Blood-breakdown products in the subarachnoid and CSF spaces may cause vasospasm.[2] Several studies have reported the positive relationship between the total amount of extravasated blood after SAH and the development of vasospasm (at that time considered the main cause of DCI) by using CT grading scales such as the modified/revisited Fisher grading scale and the Hijdra scale.[4-7] These grading scales only provide a rough estimation of the aneurysmal total blood volume (TBV) and are observer-dependent, factors that may add to the moderate prediction rates of DCI.[8] More reliable quantification of TBV might result in better prediction of DCI, which can help clinicians to more accurately identify patients at risk and to more effectively use scarce resources.[9] To assess the association of TBV with DCI, a reliable and valid method for measuring subarachnoid blood volume is needed, with correction for possible confounding influences. We recently validated a fully automatic method for TBV quantification on NCCT. This method is based on a relative density increase of blood after aSAH in relation to different brain structures.[10] In the current study, we aimed to assess the association of automatically quantified TBV with DCI.

Materials and methods

Patient population

We included consecutive patients with aSAH who were admitted between January 2009 and December 2011 to 2 large university hospitals (Academic Medical Center Amsterdam and University Medical Center Utrecht) in the Netherlands.

Aneurysmal SAH was defined as an aneurysmal bleeding pattern with an associated aneurysm. Patients without a (on CTA/MRA/DSA) proven aneurysm were excluded. We further excluded patients with a baseline CT obtained >24 hours after ictus because of the risk of blood clearance and patients in whom the CT scans could not be used for the automatic quantification method because of movement artifacts or metal artifacts caused by previous treatment. Patients with technically inadequate scans (scans in 2 parts or incomplete scans) were also excluded. Patients with an external ventricular drain on the first CT were excluded because of artifacts and possible blood clearance. TBV was defined as the sum of subarachnoid (cisternal and sulcal), intraparenchymal, intraventricular, and subdural blood.

Clinical and imaging data collection

All baseline characteristics of the included patients were collected through retrospective review of the clinical charts by a single observer (C.S.G.). These included age, medical history of hypertension, date of the aSAH ictus, hospital admission date, clinical condition on admission according to the World Federation of Neurological Societies scale (WFNS),[11] NCCT date, the occurrence of rebleeding (clinical, not CT-confirmed, or radiologic), aneurysm location (anterior or posterior circulation), aneurysm treatment (coiling, clipping, or no aneurysm treatment), and date of death. The WFNS score on admission was dichotomized into favorable (1–3) and unfavorable (4 –5). This observer also assessed the presence of clinical DCI, which was defined as clinical deterioration that could not be explained by any cause other than DCI, and radiologic DCI, which was defined as the presence of cerebral infarction on CT or MR images within 6 weeks after SAH or on the latest CT scan or MR image obtained before death, which could not be attributed to other causes such as surgical clipping or endovascular treatment, according to previously published criteria.[12] The patients were followed as long as they were hospitalized.

For the volume analysis, generally the first CT scan (all 5-mm sections) after the aSAH ictus was used. Only in case of a rebleeding within 24 hours and before treatment was the CT scan after rebleeding used because of the larger blood volume. All CT scans were anonymized before assessment (H.A.M. and I.A.Z.) and were thereafter assessed for the appropriateness for automated quantification (I.A.Z.). The TBV (in milliliters) was automatically quantified (Figure 5.1), and the quality of the automatic segmentation was evaluated by using ITK-SNAP, Version 2.4.0 (www.itksnap. org) (I.A.Z.).[13]

All CT scans were inspected for the presence of intraparenchymal hematoma (IPH) and/or intraventricular hematoma (IVH) (I.A.Z.). The presence or absence of IPH and IVH was scored dichotomously because it was not possible to measure blood volume in separate locations with our automated quantification method. The differentiation between a blood clot in the Sylvian fissure and an IPH was made on the initial CTA (I.A.Z.).[14] All estimates of blood volume and blood location were performed blinded to the presence or absence of DCI.

Statistical analysis

Descriptive statistics. Dichotomous variables were presented as percentages. Continuous variables were tested with the Shapiro-Wilk test for normal distribution ($W > 0.9$ is considered a normally distributed variable). Normally distributed variables were expressed as means with SDs, and not normally distributed variables were expressed as medians with interquartile ranges (25%–75%). Normally distributed variables were tested with the Student t test, and not

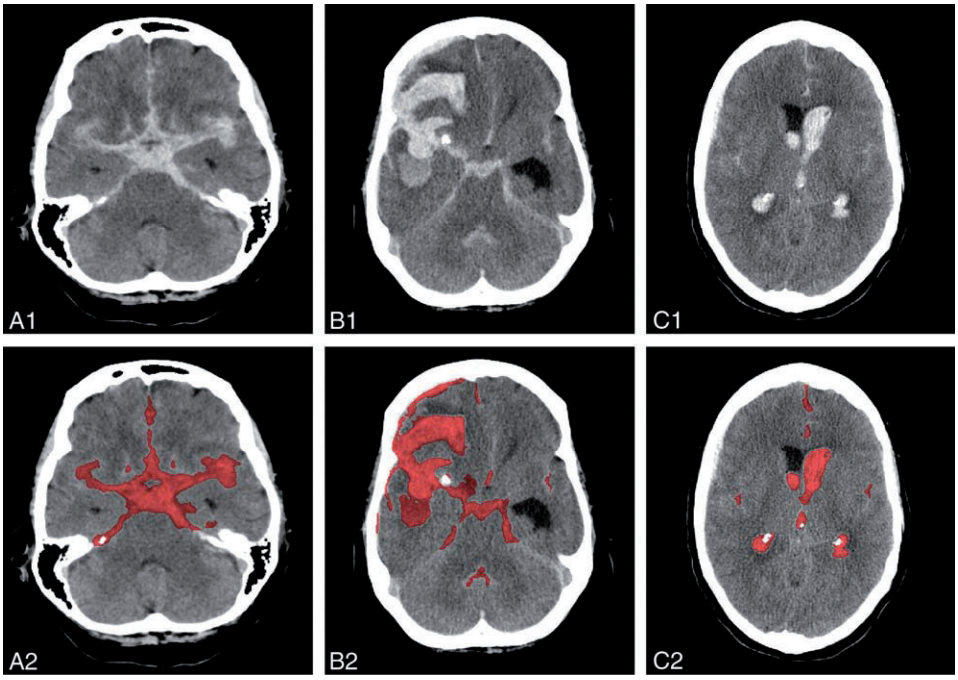

Figure 5.1. Examples of SAH bleeding patterns on CT (upper), with corresponding segmentations in red as provided by the automatic quantification method (lower).[10] A, SAH with blood in both Sylvian fissures. B, SAH with the presence of IPH. C, SAH with the presence of IVH.

normally distributed variables were tested with the Mann-Whitney U test. Categoric variables were tested by using the Fisher exact test.

Modeling. Logistic regression analysis was used to calculate odds ratios (OR) with associated 95% confidence intervals (CI). Bivariable analyses were performed with previously chosen covariables known to be associated with DCI on the basis of the literature to identify important confounders (defined as variables that changed the crude OR from the univariable analysis by >10%).[15] In the multivariable analysis, confounders were added to the univariable model to calculate adjusted odds ratios (aORs) with associated 95% CIs.

As our primary analysis, we assessed the association between TBV and clinical DCI (with or without radiologic DCI), radiologic DCI (with or without clinical DCI), and clinical and radiologic DCI (patients with both clinical and radiologic DCI) combined. Evaluated confounders were age, sex, neurologic status on admission (dichotomized WFNS grade), treatment of the aneurysm (clipping/coiling/no treatment), rebleeding, hypertension, IPH, and IVH.

As a secondary analysis, we assessed the association between blood location (IPH and IVH) and clinical DCI (with or without radiologic DCI). We used clinical DCI as the only outcome variable because we found similar aORs for all 3 outcome variables (clinical DCI, radiologic DCI, and both) in the primary analysis. Evaluated confounders were age, sex, neurologic status on admission (dichotomized WFNS grade), treatment of the aneurysm (clipping/coiling/no treatment), rebleeding, hypertension, blood volume, IPH (in the model with IVH as the central determinant), and IVH (in the model with IPH as the central determinant).

Because patients who die within 3 days after the aSAH ictus have a much lower risk of developing DCI, we performed sensitivity analyses in the subset of patients who survived >3 days after aSAH.

Results

Patient characteristics

We initially evaluated 458 potentially eligible patients with aSAH. Of these, 333 patients were included in the analyses (Figure 5.2). The mean TBV was 46.1 ± 29.4 mL. Characteristics of the included patients are shown in Table 5.1.

Sixty-eight (20%) patients had clinical and/or radiologic DCI, 62 (19%) had clinical DCI (with or without radiologic DCI), 40 (12%) had radiologic DCI (with or without clinical DCI), and 34 (10%) had both clinical and radiologic DCI. Twenty-eight (8%) patients had only clinical DCI, and 6 (2%) had only radiologic DCI (Table 5.2). One (2.1%) patient developed clinical signs of DCI 2 days after the aSAH ictus. There were 102 patients (31%) with IPH, 203 patients (61%) with IVH, and 63 patients (19%) with IPH and IVH combined. Forty-seven (14%) patients died within 3 days of the aSAH ictus. The mean TBV in these patients was 63.0 ± 34.1 mL.

Association between blood volume and blood location and DCI in the total group

The aOR (95% CI) of TBV and DCI (clinical, radiologic, both) was 1.02 (1.01–1.03) per milliliter of blood (Table 5.3). The aOR (95% CI) of IPH and clinical DCI was 0.47 (0.24–0.95) and of IVH and clinical DCI, 2.66 (1.37–5.17).

Sensitivity analysis

In the 286 patients included in the sensitivity analyses, the mean TBV was 43.3 ± 27.6 mL. In the subgroup of patients without clinical DCI, the mean TBV was 40.8 ± 27.2 mL, and in the

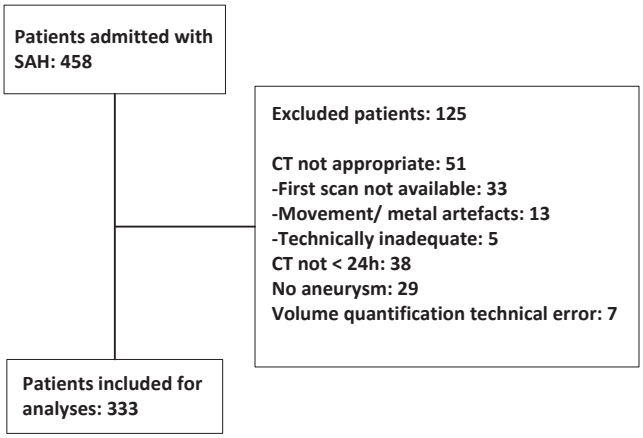

Figure 5.2. Flow chart of patient inclusion.

Table 5.1. Patient characteristics

	Total patient group (%)	Patients with clinical and/or radiologic DCI (%)	Patients without DCI (%)	p-value
No.	333	68 (20)	265 (80)	–
Female sex	238 (71)	47 (69)	191 (72)	0.653
Age (mean) (SD)	55.7 (11.9)	56.0 (12.7)	55.7 (11.7)	0.828
Hypertension in medical history	88 (26)	24 (35)	64 (24)	0.090
WFNS favorable on admission (I–III)	163 (49)	34 (50)	129 (49)	0.892
Mean TBV (mL) (SD)[a]	46.1 (29.4)	51.6 (27.3)	44.6 (29.8)	0.080
IPH	102 (31)	16 (24)	86 (32)	0.185
IVH	203 (61)	51 (75)	152 (57)	0.008
IPH and IVH	63 (19)	12 (18)	51 (19)	0.863
Rebleed	52 (16)	9 (13)	43 (16)	0.708
Anterior circulation	245 (74)	50 (74)	195 (74)	1.000
Posterior circulation	88 (26)	18 (26)	70 (26)	
Neurosurgical treatment[b]	141 (42)	30 (44)	111 (42)	0.325
Endovascular treatment[c]	135 (41)	36 (53)	99 (37)	
Death within 3 days	47 (14)	1 (1)	46 (17)	< 0.001

[a] Automatically quantified total blood volume on noncontrast CT.
[b] Two patients treated with bypass surgery.
[c] One patient treated with stent, and 1 with parent vessel occlusion.

subgroup of patients with clinical DCI, 52.3 ± 27.5 mL (p = 0.004). IPH occurred in 85 (30%) patients; IVH, in 172 (60%) patients. The association results in the sensitivity analysis (Table 5.4) are similar to the results in the total group (Table 5.3).

Table 5.2. Patient characteristics in groups with respect to DCI

	Patients with clinical and/or radiologic DCI (%)	Patients with clinical DCI (%)[a]	Patients with radiologic DCI (%)[b]	Patients with clinical and radiologic DCI (%)
No.	68 (20)	62 (19)	40 (12)	34 (10)
Female sex	47 (69)	43 (69)	28 (70)	24 (71)
Age (mean) (SD)	56.0 (12.7)	55.4 (12.9)	57.9 (12.4)	57.1 (12.8)
Hypertension in medical history	24 (35)	21 (34)	18 (45)	15 (44)
WFNS favorable on admission (I–III)	34 (50)	30 (48)	18 (45)	14 (41)
Mean TBV (mL) (SD)[c]	51.6 (27.3)	52.1 (27.4)	53.2 (28.1)	54.3 (28.3)
IPH	16 (24)	14 (23)	7 (18)	5 (15)
IVH	51 (75)	47 (76)	31 (78)	27 (79)
IPH and IVH	12 (18)	10 (16)	5 (13)	3 (9)
Rebleed	9 (13)	9 (15)	6 (15)	6 (18)
Anterior circulation	50 (74)	45 (73)	28 (70)	23 (68)
Posterior circulation	18 (26)	17 (27)	12 (30)	11 (32)
Neurosurgical treatment[d]	30 (44)	28 (45)	19 (48)	17 (50)
Endovascular treatment[e]	36 (53)	33 (53)	19 (48)	16(47)
Death within 3 days	1 (1)	1 (2)	1 (3)	1 (3)

[a] Clinical DCI with or without radiologic DCI.
[b] Radiologic DCI with or without clinical DCI.
[c] Automatically quantified total blood volume on noncontrast CT.
[d] Two patients treated with bypass surgery.
[e] One patient treated with stent, and 1 with parent vessel occlusion.

Table 5.3. Associations between blood volume and blood location and DCI in the total group (N = 333)

Dependent variable	Central determinant	OR (95% CI)	aOR (95% CI)
Clinical DCI (with or without radiologic DCI)	TBV[a]	1.01 (1.0–1.02)[b]	1.02 (1.01–1.03)[b]
	IPH[c]	0.61 (0.32–1.16)	0.47(0.24–0.95)
	IVH[d]	2.31 (1.23–4.33)	2.66 (1.37–5.17)
Radiologic DCI (with or without clinical DCI)	TBV[e]	1.01 (1.0–1.02)[b]	1.02 (1.01–1.03)[b]
Clinical and radiologic DCI	TBV[f]	1.01 (1.0–1.02)[b]	1.02 (1.01–1.03)[b]

[a] Confounders: age, WFNS, treatment, IPH, and IVH.
[b] Per milliliter of blood.
[c] Confounder: treatment.
[d] Confounders: WFNS and blood volume.
[e] Confounders: age, treatment, IPH, and IVH.
[f] Confounder: treatment, IPH, and IVH.

Table 5.4. Associations between blood volume and blood location and DCI in patients who survived 3 days or more (n = 286)

Dependent variable	Central determinant	OR (95% CI)	aOR (95% CI)
Clinical DCI (with or without radiologic DCI)	TBV[a]	1.01 (1.00–1.03)[b]	1.02 (1.01–1.03)[b]
	IPH[c]	0.65 (0.33–1.25)	0.43 (0.21–0.89)
	IVH[d]	2.41 (1.27–4.57)	2.03 (1.05–3.92)
Radiologic DCI (with or without clinical DCI)	TBV[a]	1.01 (1.00–1.03)[b]	1.02 (1.01–1.03)[b]
Clinical and radiologic DCI	TBV[a]	1.02 (1.00–1.03)[b]	1.02 (1.01–1.03)[b]

[a] Confounders: IPH and IVH.
[b] Per milliliter of blood.
[c] Confounders: WFNS, blood volume, and IVH.
[d] Confounder: blood volume.

Discussion

In this study, a higher TBV, quantified with a fully automated method, was significantly associated with the development of DCI. The presence of an intraventricular hematoma was also positively associated with the development of DCI, whereas the presence of an intraparenchymal hematoma was negatively associated with DCI.

The association between TBV and DCI may appear small with an aOR of 1.02 per milliliter of blood. However, considering that the aOR is per milliliter of blood and that in our population, the mean TBV was 46.1 mL and the SD was almost 30 mL, this effect is substantial: A difference of 1 SD of TBV (30 mL) corresponds to an aOR of 1.81.

In both analyses assessing the association between TBV and DCI, we found similar aORs for all 3 outcome variables (clinical DCI, radiologic DCI, and both). This finding could justify using 1 outcome variable in future studies. Clinical DCI would be the most appropriate to use because almost all patients with radiologic DCI have clinical DCI. Moreover, the importance of radiologic DCI in the absence of clinical DCI is questionable. CT or MR imaging might be performed for other reasons, showing areas of ischemia that are clinically unnoticed.

In the first publication on the relation between the amount and distribution of subarachnoid blood detected on NCCT and cerebral vasospasm (detected on angiography), it was concluded that blood localized in the subarachnoid space in sufficient amounts at specific sites is the only important etiologic factor in vasospasm.[4] Because in our study we found an association of TBV, IPH, and IVH with clinical and radiologic DCI and not vasospasm, these studies are difficult

to compare. One large difference is that in their study, not 1 patient with IVH developed clinical symptoms of DCI.

Only 1 more recent study investigated a semiautomatic blood quantification to assess the association between cisternal blood volume on NCCT and vasospasm after aSAH.[16] In this study, a positive association was found. However, the method used was laborious because all blood was outlined manually. Moreover, no correction for potential confounders was performed.

Our study results are in line with results from other studies showing that patients without intraventricular blood and with a small amount of cisternal blood after aSAH are less likely to develop DCI, though the results are somewhat different because these studies used vasospasm as an end point instead of DCI.[6,7] Nevertheless, these studies used the modified Fisher score instead of quantified blood volume to assess the amount of intracranial blood.[4]

The positive association between IVH and DCI is not yet understood. Blood can migrate toward the ventricles in 2 ways: first, straight from the aneurysm into the ventricles through a connecting hematoma or, second, by expansion of the subarachnoid blood toward one of the cisternal-ventricular foramina (Luschka, Magendie). The latter implies an initially higher volume of subarachnoid blood, with secondary ventricular redistribution. This might explain the association of IVH and DCI in this specific population. Additionally, patients who present with a nonaneurysmal IVH have a very low risk of developing DCI according to a study describing a series of patients with ruptured arteriovenous malformations, of whom 50 had an intraventricular component. Only 1 patient who also had an SAH component developed vasospasm, without signs of DCI.[17] According to these and our results, it seems that the combination of IVH and aSAH is worse than IVH or aSAH alone.

When one tries to explain the negative association of the presence of an IPH with clinical DCI, it could very well be that in these patients, clinical DCI was less often detected because they already had a neurologic deficit due to the IPH. To our knowledge, there is no literature confirming this theory. Further studies are needed to confirm this and to determine the association between IVH and IPH and DCI. In such a study, blood volume values for each separate compartment can be determined and subsequently associated with the clinical course.

The strengths of our study are fast and objective estimation of the TBV by using a validated automatic quantification method, adjustment for confounders to make the estimation of the association more reliable, and performance of a sensitivity analysis to evaluate the robustness of the model. In addition, we used DCI as an outcome variable instead of vasospasm because DCI is a more clinically relevant outcome measure and because vasospasm and DCI can occur

independently.[2,12] In future studies, it might be possible to use the automated quantification method to study other subtypes of SAH (eg, due to intracranial dissection, AVM, benign perimesencephalic hemorrhage, and trauma).

Our study has some limitations. This was a retrospective study in which we could only study the data that were available in the clinical charts and on the available NCCTs. Because patients were followed up only during hospitalization, we may have potentially missed patients with DCI after discharge. In patients with clinical rebleeding within 24 hours after aSAH ictus, we might have underestimated the blood volume because this rebleeding was not CT-confirmed. Death during admission may be a competing risk for the development of DCI. Unfortunately, due to the composition of our data, we were unable to perform a reliable competing risk analysis.

Limitations of the automated quantification method are that imaging artifacts can make the results unreliable. Although we do not expect differences in the detection rate of TBV and aSAH between the anterior and posterior circulations, we have not yet investigated this possibility. Very small blood volumes with low density are not well-detected with automated detection.[10] The volume assessments were performed on relatively thick sections of 5 mm. Thinner sections could potentially increase accuracy. However, with thinner sections, the noise level increases as well, which may actually reduce the accuracy. The method was validated by using 5-mm sections, and 5 mm is the standard section thickness used in our hospital and the referring centers. The volume of the IPH and IVH and the blood volume in separate territories could not be separately delineated.

Conclusions

We show that a higher TBV, measured with our automated quantification method, is significantly associated with DCI. The results of this study encourage the use of rater-independent quantification methods in future multicenter studies on DCI prevention and prediction.

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Association of quantified location-specific blood volumes with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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Abstract

Background and purpose: Delayed cerebral ischemia is a severe complication of aneurysmal SAH and is associated with a high case morbidity and fatality. The total blood volume and the presence of intraventricular blood on CT after aneurysmal SAH are associated with delayed cerebral ischemia. Whether quantified location-specific (cisternal, intraventricular, parenchymal, and subdural) blood volumes are associated with delayed cerebral ischemia has been infrequently researched. This study aimed to associate quantified location-specific blood volumes with delayed cerebral ischemia.

Materials and methods: Clinical and radiologic data were collected retrospectively from consecutive patients with aneurysmal SAH with available CT scans within 24 hours after ictus admitted to 2 academic centers between January 2009 and December 2011. Total blood volume was quantified using an automatic hemorrhage-segmentation algorithm. Segmented blood was manually classified as cisternal, intraventricular, intraparenchymal, or subdural. Adjusted ORs with 95% confidence intervals for delayed cerebral ischemia per milliliter of location-specific blood were calculated using multivariable logistic regression analysis.

Results: We included 282 patients. Per milliliter increase in blood volume, the adjusted OR for delayed cerebral ischemia was 1.02 (95% CI, 1.01–1.04) for cisternal, 1.02 (95% CI, 1.00–1.04) for intraventricular, 0.99 (95% CI, 0.97–1.02) for intraparenchymal, and 0.96 (95% CI, 0.86–1.07) for subdural blood.

Conclusions: Our findings suggest that in patients with aneurysmal subarachnoid hemorrhage, the cisternal blood volume has a stronger relation with delayed cerebral ischemia than the blood volumes at other locations in the brain.

Introduction

Although case fatality rates have been declining during the past years, aneurysmal subarachnoid hemorrhage (aSAH) is still a devastating disease with a case fatality of approximately 30%.[1] Delayed cerebral ischemia (DCI) is a severe complication that occurs in approximately 20%–30% of patients and is associated with high morbidity and mortality.[2] One of the strongest predictors of DCI is the amount of blood on the admission CT scan.[3-6]

Apart from the amount of extravasated blood, the break-through of blood from the subarachnoid cisterns into the ventricle system is also associated with the occurrence of DCI. Various studies have shown that the presence of an intraventricular hemorrhage (IVH) in patients with aSAH is an independent risk factor for DCI.[5,7-11] However, conflicting results regarding the association between the presence of intraparenchymal hemorrhage (IPH) and DCI in patients with SAH are found.[9,11-14] The occurrence of subdural hemorrhage (SDH) is relatively rare after SAH, and its association with DCI is currently unknown.[15]

Although various studies determined the association between the presence of IVH or IPH and DCI, only a few studies associated estimates of these volumes with DCI. One study found an association between IVH volume and DCI.[6] However, a more recent study did not confirm this finding.[16] The only study that determined IPH volume in patients with aSAH found no association with DCI.[5] These studies used radiologic scales such as the Hijdra sum score to estimate the cisternal blood volume, the IVH score for IVH volume, and the ABC/2 score for IPH volume.[6,17,18] These radiologic scales are not very accurate and are shown to have poor-to-moderate interobserver agreement, limiting their discriminative power.[16,19] Moreover, the ABC/2 score has been shown to overestimate the IPH volume.[20]

Quantitative measures have the promise of more precisely assessing blood volumes. Previous studies have found a strong relation between the quantified amount of total blood volume and DCI.[9,21] However, in these studies, the volumes of blood in the separate compartments of the brain were not analyzed separately. It is therefore currently unknown whether taking the blood volumes at these locations into account improves the prediction of DCI. In this study, we took the first step in addressing this issue by quantifying the cisternal, intraventricular, intraparenchymal, and subdural blood volumes separately and determining their independent associations with DCI.

Materials and methods

Population

We included patients from a retrospectively collected cohort consisting of all patients with aSAH admitted to the Academic Medical Center Amsterdam and University Medical Center Utrecht, the Netherlands, between January 2009 and December 2011.[9] Inclusion criteria were the following: 1) SAH proved on noncontrast CT; 2) aneurysm proved on either CTA, MRA, or DSA; and 3) NCCT performed within 24 hours after ictus and available for review. Patients who did not survive the first 3 days after SAH onset were excluded. Furthermore, patients with NCCTs whom we could not use for hemorrhage quantification, for instance due to movement and/or metal artifacts from previous treatment, were excluded.[22]

Clinical data

Collected demographic and clinical variables were the following: age, sex, history of hypertension, neurologic condition on admission (according to the World Federation of Neurosurgical Societies [WFNS] scale),[23] time between ictus and admission, location of the aneurysm (anterior or posterior circulation) and treatment technique (no aneurysm treatment, clipping, or coiling), rebleeding, and the occurrence of clinical DCI during admission. Aneurysms of the posterior communicating artery were allocated to the posterior circulation.

Delayed cerebral ischemia

DCI was defined as the occurrence of new focal neurologic impairment or a decrease on the Glasgow Coma Scale score that could not be explained by any other cause. A CT scan of the brain was performed to rule out hydrocephalus, and blood was sampled to exclude a metabolic encephalopathy, such as infection or electrolyte disturbances, to exclude other causes of neurologic deterioration. An electroencephalogram was obtained in case of suspicion of seizures.[24] DCI was diagnosed by the treating physician who could be either a neurologist, neurosurgeon, or intensivist. A new cerebral infarct on follow-up CT, which could not be attributed to surgical clipping, endovascular treatment, or drain placement, was supportive but not required for the diagnosis of DCI (Online Figure). The standard care to prevent DCI was similar in both participating centers. All patients received nimodipine (6 times daily, 60 mg orally) and intravenous fluids aiming at normovolemia. The mean arterial pressure was kept above 65 mm Hg. Furthermore, if the patient used antihypertensive medication, it was stopped at admission.

Image analysis

The first scan after ictus was used for the analysis. However, if rebleeding occurred within 24 hours, the scan after rebleeding was used. All scans were reviewed for the presence of cisternal blood, IVH, IPH, and SDH by 2 observers (I.A.Z. and W.E.v.d.S.). The hemorrhage was segmented on admission NCCT using an automatic hemorrhage-segmentation algorithm.[22] All segmentations were checked and, if needed, manually corrected using ITK-SNAP, Version 3.4.0 (www.itksnap.org) by a trained observer (W.E.v.d.S.) who was blinded to outcome.[25] From this segmentation, the total blood volume was calculated in milliliters. Subsequently, segmented blood was classified as cisternal, intraparenchymal, intraventricular, or subdural by manually outlining the ventricular, intraparenchymal, and/or subdural part of the segmented total hemorrhage by a trained observer (W.E.v.d.S.) (Figure 6.1). If part of the SAH was in

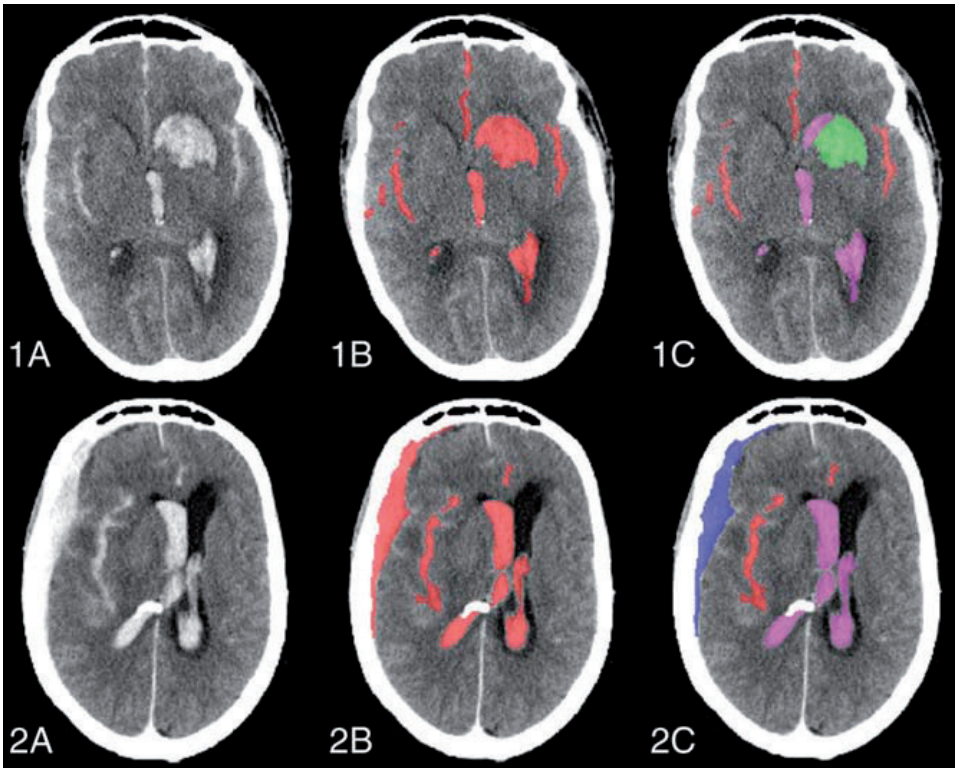

Figure 6.1. Classification of the total blood volume as cisternal, intraventricular, intraparenchymal, and subdural. 1A, Axial slice of a noncontrast CT of a patient with aSAH with concomitant IVH and IPH. 1B, Quantified total blood volume. 1C, Classified cisternal (red), intraventricular (magenta), and intraparenchymal (green) blood. 2A, Axial slice of a noncontrast CT scan of a patient with aSAH with concomitant IVH and SDH. 2B. Quantified total blood volume. 2C, Classified cisternal (red), intraventricular (magenta), and subdural (blue) blood.

proximity of the Sylvian fissure and not clearly located inside of the fissure on NCCT, the CTA was evaluated to differentiate the cisternal and intraparenchymal part of the hematoma.[26] If contrast-enhanced vessels were present in the hematoma on CTA, this part was classified as cisternal. If no vessels were detected, it was classified as IPH. The classifications were checked by a second observer, an experienced radiologist (I.A.Z.). After we classified the blood as cisternal, intraparenchymal, intraventricular, or subdural, the location-dependent volumes could be calculated by multiplying the number of classified voxels by its voxel size.

Statistical analysis

Baseline variables were compared between patients with and without DCI using the Fisher exact test for dichotomous and categoric variables, the independent samples t test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. Variables were checked for normality using the Shapiro-Wilk test (W > 0.9 was considered normally distributed).

Correlations between the cisternal blood volume and IVH, IPH, and SDH volume were calculated using the Spearman rank correlation coefficient.

Univariable logistic regression analysis of the total blood; cisternal blood; and IVH, IPH, and SDH volume with DCI was performed to determine ORs with 95% confidence intervals for DCI per milliliter of blood.

Associative models for the cisternal, IVH, IPH, SDH, and total blood volume were created by calculating adjusted odds ratios (aORs) by separately adding potential confounders to the univariable model. Variables that changed the OR of the univariable model by > 10% were considered confounders and were included in the final associative model. Potential confounders were age, sex, neurologic condition on admission (WFNS grade), treatment technique (no treatment, clipping, or coiling), rebleeding, and hypertension in accordance with previous literature.[9,27] For the 4 associative models of cisternal, IVH, IPH, and SDH volume, the remaining 3 volumes were also included in the confounding analysis. In the associative model of the total volume, the location-dependent volumes were not added as confounders because the total volume consisted of these volumes.

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, Version 23.0.0.2 (IBM, Armonk, New York).

Results

Of the 458 patients who were evaluated for study inclusion, 176 patients were excluded because of the following reasons: NCCT not available (n = 33); NCCT not suitable for assessment because of movement and/or metal artifacts (n = 13) or other technical reasons (n = 16); the first NCCT not performed within 24 hours (n = 38); no aneurysm found on CTA, MRA or DSA (n = 29); and death within 3 days after SAH onset (n = 47).[9]

Characteristics of the 282 included patients are shown in Table 6.1 for the total study population and stratified by DCI group. The mean age was 55.8 ± 12.0 years, and 73% were female. In this cohort, 61 (22%) patients developed DCI. Patients with DCI had larger total (p = 0.01) and cisternal (p < 0.001) blood volumes (Figure 6.2), more frequently had an IVH (p = 0.003), and had a larger IVH volume (p = 0.01).

There was a weak positive correlation between cisternal and IVH blood volumes (Spearman p = 0.15, p = 0.01), a weak negative correlation between cisternal and IPH blood volumes (Spearman p = -0.16, p = 0.01), and no correlation between cisternal and SDH blood volumes.

In the univariable analysis, both the total blood volume (OR = 1.02; 95% CI, 1.01–1.03) per milliliter increase in volume and the cisternal blood volume (OR = 1.02; 95% CI, 1.01–1.04) were significantly associated with DCI. After correction for confounders, the total (aOR = 1.02; 95% CI, 1.01–1.03) and cisternal (aOR = 1.02; 95% CI, 1.01–1.04) blood volumes remained significantly associated with DCI.

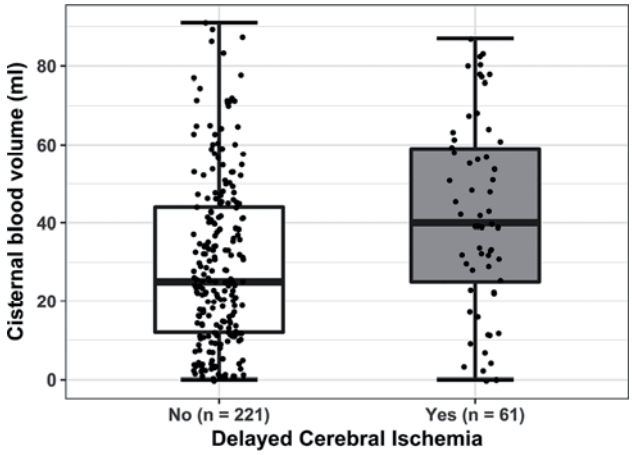

Figure 6.2. Dot boxplot of quantified cisternal blood volume in patients with and without DCI.

Table 6.1. Patient characteristics

Parameter	All (n = 282)	No DCI (n = 221)	DCI (n = 61)	p-value
Age (mean) (± SD)	55.8 (12.0)	55.9 (11.8)	55.4 (13.0)	0.80
Female sex (No.)	205 (73%)	163 (74%)	42 (69%)	0.52
History of hypertension (No.)	79 (28%)	58 (26%)	21 (34%)	0.26
Aneurysm location (No.)				0.62
Anterior	212 (75%)	168 (76%)	44 (72%)	
Posterior	70 (25%)	53 (24%)	17 (28%)	
WFNS grade (No.)				0.08
1	79 (28%)	68 (31%)	11 (18%)	
2	67 (24%)	50 (23%)	17 (28%)	
3	8 (3%)	6 (3%)	2 (3%)	
4	68 (24%)	56 (25%)	12 (20%)	
5	59 (21%)	40 (18%)	19 (31%)	
Treatment modality (No.)				0.23
No treatment	14 (5%)	13 (6%)	1 (2%)	
Clipping	138 (49%)	111 (50%)	27 (44%)	
Coiling	130 (46%)	97 (44%)	33 (54%)	
Rebleeding (No.)	34 (12%)	26 (12%)	8 (13%)	0.83
Total blood volume (median) (IQR)	41.2 (23.6–62.5)	37.7 (21.8–57.9)	52.1 (34.5–78.1)	0.01
Cisternal blood volume (median) (IQR)	29.8 (14.0–47.0)	25.2 (12.4–44.1)	39.7 (24.2–60.1)	< 0.001
IVH presence (No.)	187 (66%)	137 (62%)	50 (82%)	0.003
IVH volume (median) (IQR)	0.7 (0.0–2.8)	0.5 (0.0–2.2)	1.2 (0.3–5.0)	0.01
IPH presence (No.)	85 (30%)	70 (32%)	15 (25%)	0.35
IPH volume (median) (IQR)	0.0 (0.0–3.3)	0.0 (0.0–3.6)	0.0 (0.0–0.8)	0.29
SDH presence (No.)	16 (6%)	12 (5%)	4 (7%)	0.76
SDH volume (median) (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.74

DCI, delayed cerebral ischemia; WFNS, World Federation of Neurosurgical Societies; IVH, intraventricular hemorrhage; IPH, intraparenchymal hemorrhage; SDH, subdural hemorrhage.

In both the univariable and multivariable analysis, no statistically significant associations were found among the IVH volume (aOR = 1.02; 95% CI, 1.00–1.04), IPH volume (aOR = 0.99; 95% CI, 0.97–1.02), SDH volume (aOR = 0.96; 95% CI, 0.86–1.07), and DCI (Table 6.2).

Table 6.2. Association of blood volumes and DCI per milliliter increase in volume

Variable	OR (95% CI)	aOR (95% CI)
Total blood volume	1.02 (1.01–1.03)*	1.02 (1.01–1.03)[a]*
Cisternal blood volume	1.02 (1.01–1.04)*	1.02 (1.01–1.04)[b]*
IVH volume	1.02 (1.00–1.04)	1.02 (1.00–1.04)[c]
IPH volume	0.99 (0.97–1.01)	0.99 (0.97–1.02)[d]
SDH volume	0.96 (0.85–1.08)	0.96 (0.86–1.07)[e]

* Statistically significant.
DCI, delayed cerebral ischemia; IVH, intraventricular hemorrhage; IPH, intraparenchymal hemorrhage; SDH, subdural hemorrhage.
[a] Confounders: none.
[b] Confounders: none.
[c] Confounders: WFNS, cisternal blood volume
[d] Confounders: WFNS, cisternal blood volume, and IVH volume.
[e] Confounders: WFNS, treatment, cisternal blood volume, IVH volume, and IPH volume.

Discussion

In this study, we associated location-specific blood volumes with the occurrence of DCI. In our population, increasing cisternal blood volume was associated with a higher risk of DCI. This relation was not found with intraventricular, intraparenchymal, and subdural blood volume.

Our results confirm that larger amounts of blood in the subarachnoid space are associated with a higher chance of DCI.[3,5,9,21,28] The IVH volume was not significantly associated with DCI, though the point estimate of the aOR was like that of the cisternal volume, which may indicate a lack of power to show a statistically significant effect. The only other study that quantified IVH volume showed a higher median IVH volume in patients with DCI compared with patients without DCI.[28] In our study, patients with DCI also had a higher median IVH volume. Two other studies that used qualitative scores to assess IVH volume in patients with SAH found that a higher ventricular clot volume was independently associated with a higher risk of DCI.[5,6] Another study that included only patients with aSAH with concomitant IVH showed no association between IVH volume and DCI.[16] Our findings neither support nor reject the hypothesis that IVH volume is related to the occurrence of DCI.

We found no association between IPH volume and DCI, similar to findings of the only other study that assessed IPH volume.[5] Recently, 2 studies found an association between the presence of an IPH and DCI.[12,13] However, in both studies, a new ischemic lesion was used as the end point instead of clinical DCI. Not all patients with clinical DCI will develop a cerebral infarct, making the results of these studies difficult to compare with those of our study.[29]

Moreover, the presence rather than the volume of IPH was considered in these studies. The SDH volume has not been previously associated with the occurrence of DCI, to our knowledge.

Our results show a difference between cisternal and IVH volumes on the one hand and IPH and SDH volumes on the other in relation to DCI. A possible explanation might be that the ventricles are an overflow compartment of the cisterns. A larger volume of blood in the ventricles may actually result from a larger cisternal blood volume that has either been directly released into the ventricles or has been redistributed via the foramina of Luschka and possibly via the interpeduncular cistern.[30] However, in our data, only a weak correlation between the cisternal blood volume and the IVH volume was found. Intraparenchymal and subdural hematomas, on the other hand, are a more direct extension of blood from the aneurysm without an interstitial subarachnoid compartment. The underlying mechanism causing DCI (cerebral vasospasm, microthrombosis, microvascular spasm, inflammation, and/or cortical spreading ischemia) has been thought to be related to both rupture of an intracranial aneurysm and to blood being released into the subarachnoid space containing CSF.[31] The latter may not apply to the intraparenchymal compartment. This possibility may explain the absence of a relation between the IPH and SDH volumes and the occurrence of DCI. Furthermore, a complicating factor in the assessment of clinical DCI is caused by the presence of IPH because such a hematoma can already cause a focal neurologic deficit itself. Moreover, in general, it is difficult to score DCI when the condition of a patient deteriorates shortly after the aneurysm treatment, while the new hypodensity surrounding the initial hematoma on a CT scan can also be caused by edema or infarction due to the hematoma itself or the aneurysm treatment. This combination of factors could lead to underscoring of DCI in this time period.

An important strength of this study is the computer-assisted quantification of the volume of blood in all different compartments of the brain. With computer-assisted quantification, even a very small layering of blood could be delineated, adding to the total volume of intracranial blood. This delineation allowed a calculation of risk per milliliter of blood and a more quantitative means to assess the association with DCI as opposed to the very coarse qualitative grading scales. A remaining limitation of the computer-assisted technique up to this moment is that even though the total blood volume could be segmented automatically, the ventricular, intraparenchymal, and subdural outlines were manually drawn. This feature may lead to some observer-dependent variation. We tried to limit this by inspection of the segmentations by an experienced radiologist; however, it has been proved difficult to accurately differentiate IPH and cisternal hematoma, especially in patients with ruptured middle cerebral artery aneurysms. We tried to overcome this problem by combining the NCCT with the CTA to allow differentiation between these 2 compartments and to assess the IPH volumes.[26] Nevertheless, even with the use of CTA, some misclassification of IPH may have occurred.

A weakness of this study is its retrospective design, which may have resulted in suboptimal analysis of the clinical data. However, by including all consecutive patients in a limited time span, we have tried to minimize this bias because all patient data were analyzed in the same way.

Our results suggest that patients with high cisternal blood volume have a high risk of DCI. Thus, these patients could be a target for intensive monitoring and new prophylactic treatment strategies.[32] However, even though our study shows associations between location-specific blood volumes and DCI, the question remains as to whether these volumes improve the existing prediction models, including, for instance, the modified Fisher score.[10] If this is the case, these volumes may be of clinical value. This will have to be confirmed by the development and validation of prediction models for DCI, including the location-specific volumes. Furthermore, in this study, patients were not routinely followed up after the admission period. Thus, the correlation between the location-specific volumes and clinical outcome could not be reliably determined. Future prospective studies are warranted to answer this important remaining question. Manual selection of the IVH, IPH, or SDH region is too cumbersome to use in daily practice. Automatic region-detection techniques should be developed before this can be used as a clinical tool.

Conclusions

In our population, increasing cisternal blood volume was associated with a higher risk of DCI. This relation was not found with intraventricular, intraparenchymal, and subdural blood volume. Our findings suggest that in patients with an aSAH, the cisternal blood volume has a stronger relation to DCI than the blood volumes at other locations in the brain.

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7.

High-dose nadroparin following endovascular aneurysm treatment benefits outcome after aneurysmal subarachnoid hemorrhage

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Abstract

Background: Delayed cerebral ischemia (DCI) is one of the major causes of delayed morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Objective: To evaluate the effect of high-dose nadroparin treatment following endovascular aneurysm treatment on the occurrence of DCI and clinical outcome.

Methods: Medical records of 158 adult patients with an aSAH were retrospectively analyzed. Those patients treated endovascularly for their ruptured aneurysm were included in this study. They received either high-dose (twice daily 5700 AxaIE) or low-dose (once daily 2850 AxaIE) nadroparin treatment after occlusion of the aneurysm. Medical charts were reviewed and imaging was scored by 2 independent neuroradiologists. Data with respect to in-hospital complications, peri-procedural complications, discharge location, and mortality were collected.

Results: Ninety-three patients had received high-dose nadroparin, and 65 patients prophylactic low-dose nadroparin. There was no significant difference in clinical DCI occurrence between patients treated with high-dose (34%) and low-dose (31%) nadroparin. More patients were discharged to home in patients who received high-dose nadroparin (40%) compared to low-dose (17%; odds ratio [OR] 3.13, 95% confidence interval [95% CI] 1.36–7.24). Furthermore, mortality was lower in the high-dose group (5%) compared to the low-dose group (23%; OR 0.19, 95% CI 0.07–0.55), also after adjusting for neurological status on admission (OR 0.21, 95% CI 0.07–0.63).

Conclusion: Patients who were treated with high-dose nadroparin after endovascular treatment for aneurysmal SAH were more often discharged to home and showed lower mortality. High-dose nadroparin did not, however, show a decrease in the occurrence of clinical DCI after aSAH. A randomized controlled trial seems warranted.

Introduction

Delayed cerebral ischemia (DCI) significantly contributes to poor outcome and death in patients with aneurysmal subarachnoid hemorrhage (aSAH), and occurs in as much as 40%.[1-3] Recently, an International Survey on treatment strategies for DCI showed a wide variation in treatment practices.[4] This variability is likely to continue as the pathophysiology of DCI is still incompletely understood.[5] Heparin, a pleiotropic drug, has been shown to significantly reduce neuroinflammation, demyelination, and transsynaptic apoptosis in a subarachnoid hemorrhage (SAH) model in rats, in doses that do not produce therapeutic anticoagulation.[6,7] In a retrospective study, patients who were treated with low-dose (8 U–10 U/kg/h) intravenous heparin, started 12 hours after surgical clipping and continued to discharge, developed less DCI compared to conventional prophylactic regimens, without an increase in bleeding complications.[8] The literature on heparin reducing DCI however remains inconclusive.[9-11]

During a 2-year period, we treated aSAH patients after endovascular aneurysm treatment with high-dose nadroparin until discharge in order to prevent thromboembolic events at the level of the coiled aneurysm. The aim of this study was to assess whether these patients developed less DCI than patients who, in the period thereafter, were treated with low-dose nadroparin. Our secondary aim was to assess whether outcome was better in these patients.

Methods

Approval for this study was granted by the institutional review board with a waiver of informed consent.

Patient population

Between January 2006 and December 2008, adult patients with an aSAH, who were admitted to the Academic Medical Center (Amsterdam, the Netherlands), a tertiary referral center in the Amsterdam Metropolitan Area with a total population of approximately 2.4 million people, were included in this study if (1) SAH was confirmed by a plain computed tomography (CT)-scan on admission, or by the presence of xanthochromia in the cerebral spinal fluid (CSF), (2) a causative aneurysm was documented either by CT-angiography or digital subtraction angiography (DSA), and (3) the aneurysm was endovascularly treated.

Data collection

Clinical records, radiological investigations, and referral letters were examined. Data were collected with respect to demographic characteristics, World Federation of Neurological Surgeons (WFNS) grade[12] on admission, Fisher grade[13] as determined by an experienced neuroradiologist, recurrent bleeding (before and after treatment), occurrence of spontaneous intracranial hemorrhage, clinical DCI (cDCI), cerebral infarction on radiological imaging, hydrocephalus, location of aneurysm, per procedural complications (ie, aneurysm rupture, dissection, or arterial thrombosis), dosage of administered nadroparin, CSF drainage (ie, external CSF drainage by ventricular or lumbar catheter), implantation of permanent shunt, in-hospital complications (ie, pneumonia, meningitis, or delirium), discharge location, and in-hospital mortality.

The neurological state (WFNS grade) on admission was dichotomized into good (WFNS grade I–III) and poor (WFNS IV or V). To determine the occurrence of cDCI, we used the definition by Vergouwen et al.[14]: "The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or magnetic resonance imaging (MRI) of the brain, and appropriate laboratory studies." Spontaneous intracranial hemorrhage was defined as any radiological occurrence of an intracranial hemorrhage that was not attributable to an intervention and caused neurological deficits.

A cerebral infarction was defined as the presence of cerebral infarction on MRI 6 months after SAH, or on the latest CT- or MR-scan madebefore death within 6 months that could not be attributable to endovascular treatment or ventricular catheter placement, as based on previously published criteria.[14] If a new infarct was detected on MRI after 6 months, images were compared to the baseline and the first posttreatment scans (24–72 hours), and reviewed independently by 2 neuroradiologists (IJZ and RB) to exclude a possible other cause. If necessary, a consensus reading was done. Both radiologists were blinded to the clinical information.

Hydrocephalus was defined either by enlarged ventricles on imaging, assessed by an experienced neuroradiologist, or by increased intracranial pressure diagnosed by lumbar puncture or ventricular catheter placement. Recurrent bleeding was defined as a second (or third, etc.) bleeding from the causative aneurysm after the initial bleeding. This was determined by an increase of blood on a plain CT-scan of the head, or when a patient experienced an acute outflow

of fresh blood from their external ventricular catheter. If there was a sudden increase in blood pressure and/or a decrease in consciousness, not otherwise explained, a recurrent bleeding was suspected. Pneumonia and meningitis were scored when antibiotics were prescribed specifically for these indications. Delirium was scored if treatment with haloperidol was started and patients had a delirium observation screening (DOS)[15] above 4 or if the Richmond Agitation Sedation Scale (RASS) was scored between 4 and -4.[16]

Treatment and clinical management

In 2006 and 2007, patients with an aSAH, in whom the aneurysm was coiled, were treated twice daily with 5700 AxaIU (high-dose) low-molecular-weight nadroparin calcium (Fraxiparine, GlaxoSmithKline, United Kingdom). When a ventricular or lumbar catheter was deemed necessary, high-dose therapy was discontinued at least 12 hours before surgery and restarted within 24 hours after surgery. In January 2008, our protocol was revised, and, following current international guidelines,[17] patients were treated once daily with 2850 AxaIU (low-dose) nadroparin.

Furthermore, all patients were treated according to our standardized protocol, which was mainly based on the International Guidelines of 2002[17] and previously published by Van den Berg et al.[18] "If necessary, patients were sedated using propofol (maximum dosage of 4 mg/kg/h). Mean arterial blood pressure was kept between 80 and 130 mm Hg. If necessary, norepinephrine or labetalol was administered continuously. Nimodipine was administered in a dosage of 60 mg, 6 times daily. If enteral administration was impossible, nimodipine was given intravenously by continuous infusion (maximum dosage 48 mg/24 h). Whenever clinical signs of (delayed) cerebral ischemia occurred after occlusion of the aneurysm, hypertensive therapy with phenylephrine was initiated in an attempt to raise the cerebral perfusion pressure." This regimen was discontinued if clinical improvement was not manifest, and slowly tapered when clinical improvement was stable during a period of 24 hours. No other treatment for DCI was initiated when hypertensive therapy failed.

Ruptured aneurysms were treated preferably within 24 hours after onset of the initial aSAH. If a recurrent bleeding had occurred, patients were treated with high urgency, preferably within 1 hour, as it illustrates instability of the formed blood clot on the aneurysm.[19] An external ventricular drain, or when possible, a lumbar catheter was placed for CSF drainage in case of hydrocephalus, or if raised intracranial pressure was suspected.

Statistical analysis

For normally distributed variables (Shapiro-Wilk test) data were reported as means with standard deviations (SD). The Student's t-test was used for 2-group comparison. Unequally distributed variables, tested with the Mann-Whitney U-test, were expressed as medians with interquartile ranges (25–75%). The Chi-square or Fisher's exact test was used to assess differences in proportions wherever appropriate. Multivariate logistic regression was used for correction of baseline differences. If 10% or more of the data from a variable was missing, data from this variable were excluded from statistical analysis. Missing data were not imputed. P-values < 0.05 were considered significant. Statistical analyses were performed using the SPSS Statistics Software (version 21; IBM Corporation, Armonk, New York).

Results

The missing data percentage of most variables was under 3%, with the exception of prior drug-use (7%) and cerebral infarction (7%). If only baseline imaging and no follow-up scan was performed these items could not be scored.

Baseline characteristics

Between January 2006 and December 2008, a total of 158 consecutive aSAH patients were treated with endovascular coiling in our center. Of the 115 patients, who were treated between 2006 and 2007, 93 received high-dose nadroparin. The remaining 22 patients were treated with low-dose nadroparin, mostly because of for instance an additional neurosurgical

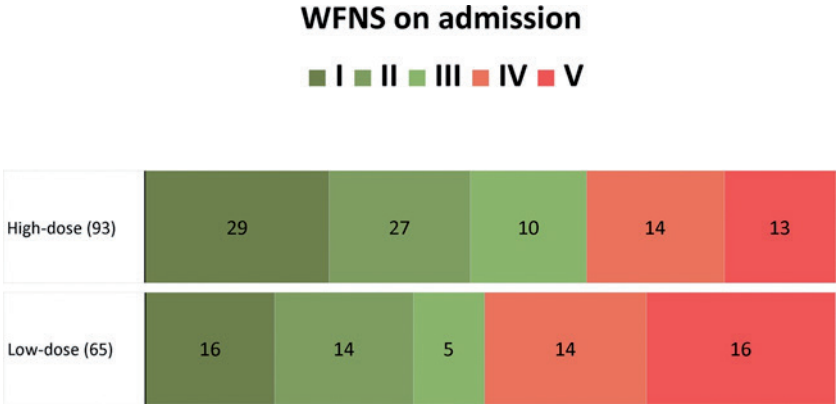

Figure 7.1. Number of patients in each WFNS score category on admission pertreatment group.

intervention that was pending after aneurysm treatment. In 2008, all but 1 patient received standard prophylactic low-dose nadroparin, conform our revised protocol. For this study, patients were allocated into 1 of 2 groups, according to their treatment dosage: high-dose or low-dose nadroparin.

There were fewer patients with a poor WFNS grade (IV or V) on admission (odds ratio [OR] 0.48, 95% confidence interval [CI]: 0.25–0.93) in the high-dose group (Figure 7.1). Furthermore there were no baseline differences between patients in both treatment groups (Table 7.1).

Table 7.1. Baseline characteristics of 158 patients with a coiled aneurysm after subarachnoid hemorrhage

		Nadroparin group		
	Total N = 158	High-dose n = 93	Low-dose n = 65	OR (95% CI)
Age in years, mean (SD)	54.1 (13.7)	53.0 (13.5)	56.0 (14.1)	0.98 (0.96–1.01)
Female	110 (70)	67 (72)	43 (66)	1.32 (0.67–2.62)
WFNS IV–V	57 (36)	27 (29)	30 (46)	0.48 (0.25–0.93)
Fisher scale score				1.04 (0.70–1.55)
1	7 (4)	2 (2)	5 (8)	
2	9 (6)	7 (8)	2 (3)	
3	34 (22)	22 (24)	12 (19)	
4	108 (68)	62 (67)	46 (71)	
Fisher 4 with IVH*	94 (60)	56 (60)	38 (59)	1.08 (0.56–2.05)
Fisher 4 with ICH*	39 (25)	21 (23)	18 (28)	0.76 (0.37–1.58)
Fisher 4 with SDH*	9 (6)	3 (3)	6 (9)	0.33 (0.08–1.36)
Aneurysm location				1.46 (0.97–2.19)
Anterior circulation	106 (67)	57 (61)	49 (75)	
Posterior circulation	18 (11)	12 (13)	6 (9)	
Multiple	34 (22)	24 (26)	10 (15)	
Medical history				
Diabetes Mellitus[#]	8 (5)	6 (7)	2 (3)	2.10 (0.41–10.77)
Cardiovascular condition[##]	19 (12)	12 (13)	7 (11)	1.20 (0.45–3.24)
Previous SAH	6 (4)	3 (3)	3 (5)	0.67 (0.13–3.41)
Drug use				
Platelet inhibitors[###]	18 (12)	12 (14)	6 (10)	1.42 (0.50–4.02)
Anticoagulation[###]	6 (4)	5 (6)	1 (2)	3.55 (0.41–31.22)
Antihypertensive drugs[#]	35 (24)	21 (24)	14 (23)	1.05 (0.48–2.27)
Statins[#]	20 (14)	12 (14)	8 (13)	1.04 (0.40–2.72)

High-dose: Nadroparin 5700 AxaIU s.c. twice-daily; Low-dose: Nadroparin 2850 AxaIU s.c. once-daily.
[#]based on n = 147; [##]based on n = 155; [###]based on n = 148. N (%) unless otherwise stated.
*Patients listed in these subcategories can overlap with each other.

Complications

There were no differences in the occurrence of clinical DCI or cerebral infarction between both groups. In the high-dose group, cDCI occurred in 34% (OR 0.63, 95% CI 0.60–2.33) and cerebral infarction in 35% (OR 0.85, 95% CI 0.43–1.68), and in the low-dose group 31% and 38%, respectively. After adjusting for neurological status on admission, the effect of heparin on the occurrence of cDCI (adjusted OR [aOR] 1.50, 95% CI 0.73–3.11) and cerebral infarction (aOR 1.02, 95% CI 0.50–2.10) did not differ (Table 7.2). Delirium was less often diagnosed in the high-dose group compared to the low-dose group (OR 0.34, 95% CI 0.13–0.86), however after adjusting for neurological status on admission this effect was not significant (aOR 0.39, 95% CI 0.15–1.00).

Table 7.2. Complications during treatment and hospital stay in 158 patients with a coiled aneurysm after SAH

		Nadroparin group		
	Total N = 158	High-dose n = 93	Low-dose n = 65	OR (95% CI)
cDCI	52 (33)	32 (34)	20 (31)	1.18 (0.60–2.33)
Cerebral infarction[#]	53 (36)	30 (35)	23 (38)	0.85 (0.43–1.68)
Recurrent bleeding before endovascular treatment	23 (15)	14 (15)	9 (14)	1.10 (0.45–2.73)
Procedural complications				
Dissection	1 (1)	1 (1)	0 (0)	2.12 (0.09–52.97)
Thrombus	8 (5)	6 (7)	2 (3)	2.17 (0.42–11.12)
Rupture	9 (6)	5 (5)	4 (6)	0.87 (0.22–3.36)
Posttreatment				
Spontaneous ICH	5 (3)	3 (3)	2 (3)	1.05 (0.17–6.47)
Subdural hematoma	3 (2)	3 (3)	0 (0)	5.06 (0.26–99.77)
Recurrent SAH	6 (4)	3 (3)	3 (5)	0.69 (0.14–3.53)
Hydrocephalus	119 (75)	72 (77)	47 (72)	1.31 (0.63–2.72)
External CSF drainage	95 (60)	57 (61)	38 (59)	1.13 (0.59–2.15)
Pneumonia	22 (14)	14 (15)	8 (13)	1.24 (0.49–3.16)
Meningitis	34 (22)	25 (27)	9 (14)	2.25 (0.97–5.21)
Delirium	22 (14)	8 (9)	14 (22)	0.34 (0.13–0.86)

High-dose: Nadroparin 5700 AxaIU s.c. twice-daily; low-dose: Nadroparin 2850 AxaIU s.c. once-daily, cDCI, clinical delayed cerebral ischemia; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CSF, cerebral spinal fluid.
[#]Based on n = 147. N (%) unless otherwise stated.

Clinical outcome

Outcome per treatment group is presented in Table 7.3. In-hospital mortality was much lower (5%) in the high-dose group compared to the low-dose group (23%; OR 0.19, 95% CI 0.07–0.55), and remained significant, when adjusted for neurological state on admission (aOR 0.21, 95% CI 0.07–0.63). More than 40% of patients in the high-dose group were discharged home compared to 17% in the low-dose group (OR 3.39, 95% CI 1.57–7.32) and this remained significant after adjusting for neurological state on admission (aOR 3.13, 95% CI 1.36–7.24). Six patients (4%) that died in the hospital were declared brain death. The remaining 14 (9%) patients died due to withdrawal of care. Both causes of death were comparable between treatment groups.

Table 7.3. Outcome and discharge location of 158 patients with a coiled aneurysm after SAH

		Nadroparin group		
	Total N = 158	High-dose n = 93	Low-dose n = 65	OR (95% CI)
In-hospital mortality	20 (13)	5 (5)	15 (23)	0.19 (0.07–0.55)
Cause of death				
cDCI	12 (60)	4 (80)	8 (53)	0.32 (0.92–1.11)
Recurrent bleeding	5 (25)	1 (20)	4 (27)	0.17 (0.18–1.52)
Initial SAH	3 (15)	0 (0)	3 (20)	0.40 (0.33–0.49)
LOS (days), median (IQR) n = 138	17 (13–28)	18 (13–31)	17 (12–27)	1.01(0.99–1.03)
Discharge location*				
Home	49 (31)	38 (41)	11 (17)	3.39 (1.57–7.32)
Other hospital	64 (41)	36 (39)	28 (43)	0.84 (0.44–1.59)
Rehabilitation centre	14 (9)	9 (10)	5 (8)	1.29 (0.41–4.03)
Nursing home/hospice	10 (6)	5 (5)	5 (8)	0.68 (0.19–2.46)
Permanent shunt (VPS/LPS)	23 (15)	18 (19)	5 (8)	2.88 (1.01–8.21)

High-dose: Nadroparin 5700 AxaIU s.c. twice-daily; Low-dose: Nadroparin 2850 AxaIU s.c. once-daily.
*Based on n = 137; IQR, interquartile range; LOS, length of stay; SAH, subarachnoid hemorrhage; cDCI, clinical delayed cerebral ischemia; VPS, ventricular peritoneal shunt; LPS, lumbar peritoneal shunt. N (%) unless otherwise stated.

Discussion

In this study, we compared patients with aSAH who were treated with high-dose nadroparin after endovascular treatment to a standard (low-dose) treatment group. We found no difference in the occurrence of clinical DCI or cerebral infarctions between the 2 groups. However, in

the high-dose nadroparin treatment group more patients were discharged to home and had lower in-hospital mortality.

The use of heparin to reduce ischemic events after treatment of ruptured aneurysms has been promoted previously.[11,20] However, its beneficial effect on outcome and incidence of cDCI was not always confirmed.[10] Siironen et al.[10] investigated 40 mg subcutaneously administered enoxaparin compared to placebo treatment and found a negative effect on clinical outcome and also 5% intracranial bleeding in the enoxaparin treatment group. In contrast, Wurm et al.[11] showed a more positive effect of enoxaparin on angiographic vasospasm, cDCI, and clinical outcome, with fewer hemorrhagic complications in the treated group. However, as Budohoski et al.[21] described in his review "groups were not well matched for neurological condition on admission." Simard et al.[20] used intravenous low-dose heparin after clipping and found less cDCI and no radiological infarct, as assessed by CT, nor clinically significant hemorrhages, and more patients could be discharged home. Possible explanations of these mixed results are the variabilities in dosage, timing, and method of administration. In addition, the treatment effects of heparin can be highly variable depending on the subcutaneous or continuous intravenous administration.[22,23]

Our study differs from the previously reported studies, mostly because our study cohort consisted of solely endovascularly treated patients and our dosage did have, in contrast to the previously mentioned studies, an anticoagulation effect. Simard et al.[20] reported on patients who were solely surgically treated. Furthermore, their treatment protocol included intravenous heparin administration. Our treatment protocol consisted of twice-daily subcutaneous injection of nadroparin, which has a longer half-life, lower risk of bleeding, better in vivo bioavailability, and more predictable pharmacokinetic response than unfractionated heparin.[24-27] Lastly, Simard et al.[20] included only Fisher 3 patients, whilst our cohort included all Fisher grades, making our results more generalizable for the whole aSAH population.

Our data suggest that treatment with high-dose subcutaneously administered low-molecular-weight nadroparin is safe, and leads to more favorable clinical outcome, favoring discharge to home, although it did not reduce cDCI in our patient cohort.

In-hospital mortality was significantly lower in the high-dose group. Although this group consisted of fewer patients in a worse clinical condition (WFNS IV-V) on admission, high-dose nadroparin remained associated with a decreased risk of mortality and a higher possibility to be discharged from hospital to home, even after adjustment for neurological status on admission (WFNS grade). Simard et al.[20] previously found that treatment with intravenous heparin led to higher discharged to home percentages in their treatment group.

Drugs such as heparin and low-molecular-weight heparins (LWMHs) are generally used for treatment of thromboembolic disorders.[28,29] Besides its anticoagulant properties, recently, several other pharmacological and neuroprotective anti-inflammatory effects have been recognized to unfractioned heparin and LMWHs.[30] There is increasing evidence that these drugs can reduce ischemic brain injury in both early and delayed brain injury.[31] Clinical studies and experimental animal models have shown that LMWH can reduce levels of cytokines, impede cell apoptosis, and decrease inflammatory reaction to reduce ischemic brain injury and, more specifically, cerebral edema. The anti-edematous properties may improve perfusion in and around the ischemic lesions, thereby limiting ischemic infarct size. Several thrombogenic factors, like thrombin are known to disrupt the blood-brain barrier and have a destructive effect on endothelial cells. Endothelial dysfunction is one of the key mechanisms that result in loss of autoregulation and promote microvascular spasm. Inhibition of thrombin activation seems to protect the blood-brain barrier and could thus tend to inhibit the loss of autoregulation.[32-35] Combined with spreading depolarizations, which occur spontaneously in the cerebral cortex of subarachnoid hemorrhage, the ischemic damage of the penumbra exacerbates focal ischemic injury.[36-38] The anticoagulant property of heparins also prevents thrombus formation and spread of existing thrombi from spastic arteries into surrounding tissues.[39] Although the prevalence of cDCI was comparable in our patient groups, it is possible that 1 or more of these properties, acting alone or as a combined effect, may account for the neuroprotective actions of LMWH and lead to improved outcome and less mortality in our population; however, further research in a prospective, randomized trial concerning its protective effects is warranted, and being prepared.

Limitations

This study has some limitations. First of all, the retrospective nature of this study limits the reliability of the results, especially for collection of safety data. It is quite remarkable that we found little bleeding complications due to the anticoagulant dosage of nadroparin. However, this study group contains patients that were solely treated endovascularly. In case of an intervention the nadroparin was discontinued for 24 hours to reduce the risk of hemorrhage. Secondly, due to the relatively small sample size small, differences may have been overlooked, and therefore, the results should be interpreted with some caution. However, this is one of the largest series comparing high-dose versus a standard prophylactic dose in endovascularly treated patients. Thirdly, while the 6-months MRI was almost always compared to CT-scans, the number of patients with a cerebral infarction may be overrated, because MR-scans are superior to CT in detecting small and new infarcts. This limitation is difficult to circumvent as patients do not tolerate an MR-scan directly after a hemorrhage as well as a CT-scan, because of the noise and the amount of time that it takes. Fourthly, modified Rankin Scale scores after 3 or 6 months

would provide a clearer picture of long-term clinical outcome. Unfortunately, no standard 3- or 6-months outcome was assessed during regular out-clinic follow-up. Therefore, only discharge location and mortality could be objectively scored because of the retrospective nature of this study. However, it is not likely that patients who were discharged to home would deteriorate in the months thereafter. Finally, 20% of the patients who should have received high-dose nadroparin between 2006 and 2007 were treated with regular prophylactic nadroparin, mostly because a neurosurgical intervention was pending.

Conclusion

In conclusion, we found no differences in the occurrences of cDCI between high-dose and low-dose LMWH groups, which did not change after adjusting for neurological condition (WFNS grade) on admission. In-hospital mortality, however, was much lower in the high-dose nadroparin group and more patients could be discharged to home. Therefore, treatment with high-dose nadroparin after endovascular occlusion of the ruptured aneurysm might be beneficial, and currently a study protocol for a prospective, randomized controlled trial is in preparation.

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8.

General discussion and future directions

Middle cerebral artery aneurysm treatment

Surgical clipping has been long considered the best treatment for middle cerebral artery (MCA) aneurysms, because of the more difficult vascular anatomy for endovascular coiling. With the increasing experience and the improvements in the technique of coiling in the past 15 years more and more aneurysms, including MCA aneurysms, have been treated with endovascular coiling. While patients with ruptured MCA aneurysms were relatively underreported in the ISAT trial, which was published in 2005, a discussion on what is the best treatment in these patients remained.[1] Also in patients with unruptured MCA aneurysms this discussion continued. Authors of studies including patients with unruptured and ruptured MCA aneurysms sometimes advocated endovascular treatment (including the use of additional devices in more complex cases) and sometimes advocated strict microsurgical treatment.[2,3] Therefore, we performed a systematic review on patients with unruptured and ruptured MCA aneurysms that were treated with endovascular coiling or surgical clipping. We did not include patients with aneurysms that were treated with more complex techniques such as parent vessel occlusion, bypass surgery, stents and flow diverters, since patients with these complex aneurysms need individualized therapies, making them a special category of patients, difficult to compare with patients with non-complex MCA aneurysms.

Unruptured aneurysms

The results from our systematic review (**Chapter 2**) suggest that standard clipping might be preferred in patients with non-complex, unruptured MCA aneurysms. However, because of the high risk of bias, and the lack of standardized reporting in many of the included studies, these results must be interpreted with care. In addition, clinical outcome was usually assessed using outcome scales such as the modified Rankin scale and the Glasgow Outcome Scale, which were developed to assess functional outcome based on the ability to perform daily activities, but which do not take quality of life and cognitive functioning into account.[4,5]

Although there seems to be an advantage for clipping in patients with unruptured MCA aneurysms regarding mortality rate, the difference with coiling is small (0.8% versus 1.1%). The question remains whether this small difference is enough to decide to treat unruptured MCA aneurysms with clipping from now on. A reported downside of endovascular treatment might be the higher posttreatment hemorrhage rate, although the difference in our review was small and only two of the included studies on clipping reported on this subject.[6] The small advantage regarding mortality rate in our study is comparable to the (non-MCA-specific) results from the ISUIA study (2.7% after clipping and 3.4% after coiling).[7] The authors state

that the difference might be explained by the higher pretreatment morbidity rate and the older age of endovascularly treated patients, two factors which were associated with worse clinical outcome in this study, and factors we could not study in our review. In patients with MCA aneurysms smaller than 7mm, without a previous history of subarachnoid hemorrhage, the 5 years' cumulative rupture risk in the ISUIA study was 0%. With an overall procedure-related morbidity (including mortality and impaired cognitive function) rate of 10.1%–12.6% and 7.1%–9.8% after surgical and endovascular treatment, respectively, the question was raised in the ISUIA study whether treatment in these patients is to be preferred over a wait-and-see policy. The UCAS study from Japan showed similar results with a per year rupture risk of 0.31% (95% CI, 0.10–0.96) of MCA aneurysms up to 6mm.[8] It was concluded that the natural course of unruptured cerebral aneurysms depends on size, shape and location. This study did not provide specific clinical and imaging outcome rates for endovascular and surgical treatment, and the authors did not make a statement on what could be the best strategy in patients with unruptured aneurysms. A prospective trial that tried to answer this question in patients with unruptured cerebral aneurysms by comparing coiling to observation, failed because of poor recruitment.[9] More recently, the PHASES score (including population, hypertension, age, earlier SAH, size and location of the aneurysm) was developed to aid physicians and their patients in determining the risk of rupture in incidental aneurysms and in deciding whether treatment of the aneurysm is warranted.[10] As the authors state in their conclusion, this score can be used as a starting point in discussing the pros and cons of incidental aneurysm treatment, but further studies are needed to improve prediction or risks (rupture risk and aneurysm treatment risks) for an individual patient.

In conclusion, multiple factors should be taken into account before deciding to start treatment in incidentally found MCA aneurysms. The available clinical data on MCA aneurysm treatment is mostly of questionable quality and lacks standardized follow-up. Only after larger observational studies from prospectively collected databases according to generally accepted guidelines (e.g. STROBE) have been performed, a more definitive conclusion can be drawn on what is the best treatment modality and moment for these patients.[11]

Ruptured aneurysms

The results from our systematic review (**Chapter 2**) suggest that coiling might be preferred in patients with non-complex, ruptured MCA aneurysms. In the ISAT trial, a benefit was shown for endovascular treatment regarding death, dependency and disability-free survival up to 10 years after treatment, for ruptured aneurysms on all locations.[12] However, patients with more complex aneurysms, including MCA aneurysms, were relatively underrepresented in the ISAT trial. The same group of researchers showed a benefit in cognitive function after

coiling of ruptured aneurysms, without presenting any specific numbers for patients with MCA aneurysms.[13] Our results are in line with the ISAT trial showing a small advantage for endovascular treatment of ruptured MCA aneurysm, with respect to favorable outcome and mortality rate. However, in our study we could not assure that all patients were eligible for both surgical and endovascular treatment. It is possible therefore, that in the surgical group also patients with worse neurological status on admission, or with more complex aneurysms, not suitable for coiling, have been analyzed, which might have negatively influenced the favorable outcome and mortality rate after clipping. The higher post-treatment hemorrhage rate after clipping in our review remains difficult to explain. Possibly, the lack of reporting on this subject in all but two studies on clipping might have been responsible for this result. Based on the results of our review we could not draw a definitive conclusion on what is the best treatment for patients with ruptured MCA aneurysms. Therefore, we concluded that comparable to aneurysms in other locations, a multidisciplinary approach in large volume neurovascular centers is recommended, with selection of the optimal treatment modality based on the clinical condition of the patient and the morphological aspects of the aneurysm

MCA aneurysm with concomitant intraparenchymal hematoma

When a patient presents with a ruptured MCA aneurysm, and a concomitant intraparenchymal hematoma (IPH), there are several treatment options: coiling, clipping or no aneurysm treatment (wait-and-see, either with or without EVD placement treatment in patients who are in the poorest neurological condition or when an explicit "no treatment" wish exists). Coiling and clipping of the aneurysm can be preceded, or followed, by decompressive craniotomy with or without clot removal. The timing and the order in which aneurysm treatment, decompression and clot removal are performed, varies and may be a point of discussion.

The American Heart Association guidelines for the management of aneurysmal subarachnoid hemorrhage states that 'microsurgical clipping may receive increased consideration in patients presenting with large (more than 50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms'.[14] This statement is based on a single, more than 20 years old (the beginning of the coiling era), study that did not divide hematomas in volumes of more and less than 50ml.[15] Other studies that did quantify hematomas did this mostly with the ABC/2 method, a method that is known to overrate the hematoma volume.[16,17] Moreover, clinical outcome data from studies on endovascular MCA aneurysm treatment, with or without decompression and clot removal, are sparse. Therefore, we performed the study described in **Chapter 3** on patients with ruptured MCA aneurysms and a concomitant intraparenchymal hematoma treated with coiling or clipping with or without decompression and clot removal.

We found a significant difference in clinical outcome between patients with poor (GCS score < 8 and/ or abnormal pupil reactions) and good (all other patients) neurological condition on admission, regardless of the hematoma volume and the treatment strategy that was used. We did not find a significant difference between coiling and clipping, neither in patients with hematomas of more than 50 milliliters, nor in patients with hematomas of less than 50ml.

If a patient has a poor neurological condition on admission, (partly) caused by an parenchymal hematoma, urgent decompressive craniotomy, combined with clipping of the aneurysm, seems to be the better option, as this can be performed faster than decompression followed by coiling, although the clinical outcome in these patients has proven to be very poor, even after aggressive hematoma evacuation and clipping of the aneurysm.[15,18] The rationale for coiling first can be that it is safer to perform the decompression (with or without clot removal), as there is very little chance of rebleeding once the aneurysm is secured. Whether a decompression should be performed in patients with large hematomas who present with good neurological condition is unclear, and we did not find a significant difference in clinical outcome between patients with IPH's of more and less than 50 milliliters. The fact that some patients with ruptured MCA aneurysm and a large concomitant IPH are in good neurological condition can possible be explained by the hematoma location, the amount of herniation and the amount of compression it gives on vital structures, such as the basal ganglia or the brain stem. These factors were not investigated in our study (**Chapter 3**), but might be useful in the decision whether to perform a decompression, or not, in these patients. We have to be cautious to draw too strong conclusions, because of the retrospective nature of our study and the relatively small amount of patients. However, as one of the largest series available including patients treated with coiling, these results do not support the American Heart Association guidelines for the management of aneurysmal subarachnoid hemorrhage. Currently, there are no other studies comparing coiling and clipping with decompression in patients with ruptured MCA aneurysms and a concomitant IPH, making it impossible to state what is the best treatment strategy in these patients. Based on our results (**Chapter 3**) the decision to perform decompression with or without clot removal should be based more on the patients' neurological condition than on the intraparenchymal hematoma volume. Whether the decompression is preceded by coiling or clipping of the aneurysm should be decided by a multidisciplinary team. Additionally, taking all available literature into account, there is insufficient evidence for a certain hematoma volume cut-off point above which surgical decompression is mandatory in patients with ruptured MCA aneurysms.

Automatic volume quantification

The original 4-point Fisher scale was developed to predict vasospasm, based on clot thickness after aSAH on NCCT, and has become the world standard on hematoma grading. While almost all patients were graded as 3 or 4, the usability for the prediction of vasospasm was questioned.[19] To improve the prediction of vasospasm, it was modified into the modified Fisher scale, which takes thin (< 1mm) and thick (> 1mm) cisternal hemorrhage and intraventricular hemorrhage into account. This modified Fisher scale has been shown to be more accurate in predicting vasospasm, but it still leaves the interpretation of the hemorrhage to the physician reading the CT images.[20]

The Hydra scale is much more comprehensive by grading the amount of blood in several basal cisterns and fissures on NCCT, but is does not make a difference in the quantity of blood in the cisterns and fissures. Additionally, the Hijdra scale is also operator-dependent and time-consuming, making it less useful in the clinical setting.[21] A novel method to grade hemorrhage volume is the Barrow Neurological Institute scale.[22] This is a simple, and semi-quantitative, method to grade the amount of blood and predict vasospasm, based on maximal SAH thickness, categorizing patients with aSAH into five more evenly distributed classes than the Fisher scale, showing better inter- and intra-observer agreement. In an external validation analysis, this scale also appears promising as a predictor for unfavorable outcome at discharge and one-year follow-up.[23]

A possible drawback of the above-mentioned methods is that they do not provide an actual hemorrhage volume. As manual hemorrhage delineation on NCCT is very time-consuming, we developed an operator-independent, automatic, hemorrhage quantification method that provides an accurate hemorrhage volume in milliliters. In **Chapter 4** we validated this method by correlating the automatically quantified hemorrhage volumes on NCCT with manually delineated hemorrhage volumes, and by comparing the method with the most widespread used hemorrhage grading scales, i.c. the Fisher scale and the Hydra scale. The method for automatic hemorrhage volume measurement (**Chapter 4**) shows very promising correlation results with manual hemorrhage delineation. The different Fisher and Hydra scale scores showed a poor correlation with actual hemorrhage volumes in milliliters, quantified with the automated method. The automated method has some limitations as it was designed to quantify the total hemorrhage volume after aSAH including the subdural (SDH), intraventricular (IVH) and intraparenchymal hematoma (IPH). Location-specific hemorrhage quantification is not yet possible with this method. And, with a duration of five minutes per patient, it is still not fast enough to use in a clinical setting. The automated method may not recognize aneurysms and larger vessels in hematoma areas, possibly leading to (a small) overestimation of the measured

total hemorrhage volume after aSAH. Finally, the method depends strongly on image quality. After having validated the method, we tested the applicability of the method in clinical studies on patients with aSAH to study whether there is an association between precise hemorrhage volume after aSAH in milliliters with the occurrence of DCI.

Hemorrhage volume and DCI

As DCI is seen in approximately 30% of the patients suffering from aSAH, and is associated with poor clinical outcome in approximately 30% of the patients, it is an important topic.[24,25] Why patients develop DCI is still poorly understood. Although vasospasm is thought to be one of the causes of DCI, and is thought to be caused by blood breakdown products in the CSF, DCI does not occur in every patient with vasospasm, and not every patient with DCI has vasospasm.[26] As a larger aSAH volume leads to more blood breakdown products in the CSF and possibly to a higher chance of developing DCI, we studied the association of the automatically quantified total (including cisternal hemorrhage, SDH, IPH and IVH) hemorrhage volume after aSAH with the occurrence of DCI (**Chapter 5**) and the association of location-specific (cisternal, subdural, intraparenchymal and intraventricular) hemorrhage volumes with the occurrence of DCI (**Chapter 6**). These studies differ from previous studies as we used DCI as outcome measure instead of vasospasm, and we used automatically quantified hemorrhage volumes (on NCCT) in milliliter (ml) instead of a hemorrhage grading scale score.[27-29] In **Chapter 5** we found that automatically quantified total hemorrhage volume after aSAH was significantly associated with the occurrence of DCI, with an increasing association per ml of hemorrhage. In **Chapter 6** we found a significant association of the cisternal hemorrhage volume in milliliters with DCI. In accordance with other studies, the association with the occurrence of DCI was less in patients with a small cisternal hemorrhage volume and no intraventricular hemorrhage (IVH). In **Chapter 5** a significant association was found between the presence of IVH and the occurrence of DCI. However, in **Chapter 6** we did not find a significant association between the IVH volume in ml and the occurrence of DCI. A possible explanation for the positive association in **Chapter 5** is that in patients with a large cisternal hemorrhage volume the hematoma breaks through to, or is redistributed to, the ventricles and that the association found in **Chapter 5** is actually caused by a larger cisternal hemorrhage volume in patients with IVH. The finding that IVH without cisternal/ subarachnoid blood is not associated with DCI is described in a study of patients with ruptured AVM's.[30] We did not find a significant association of IPH and SDH in milliliters with the occurrence of DCI in **Chapter 6**.

A limitation of the studies described in **Chapters 5** and **6** is that the retrospective nature of our studies, and the variable clinical follow-up, resulted in missing data on clinical outcome.

Therefore, we were not able to study the association of the total hemorrhage volume after aSAH and the hemorrhage volume on different locations (SDH, IPH, IVH) after aSAH with clinical outcome. Moreover, delineating the location-specific hematoma volumes on NCCT from the total quantified hemorrhage volume is a time-consuming job not suitable for the clinical setting. Taking the results of both **Chapters 5** and **6** into account, it seems likely that only the cisternal hemorrhage volume is associated with the occurrence of DCI. This could be confirmed in a future observational study in which also the association of the total hemorrhage volume after aSAH and the hemorrhage volume on different locations (SDH, IPH, IVH) after aSAH with clinical outcome can be studied.

Nadroparin and DCI

Although the prediction of DCI can be important in selecting patients needing intensive care, prevention and treatment of DCI after aSAH are at least equally important. Prevention and treatment of DCI is difficult since the pathophysiology of DCI is still poorly understood. In the past, vasospasm was thought to be the main cause. Nowadays, many pathophysiological pathways, including microthrombosis and neuroinflammation are thought to play a role in the development of DCI.[25] Heparin (LMW or unfractionated) has shown to have neuroprotective characteristics after induced ischemia in animal studies, by reducing edema and improving microvascular perfusion through several pathophysiological pathways.[31-34] It has also been shown to reduce transsynaptic apoptosis and neuroinflammation in rat brains.[35] Two prospective, randomized clinical studies on the use of subcutaneously injected low-dose Enoxaparin (a LMWH) showed mixed results on the effects on clinical outcome and the occurrence of DCI in patients with ruptured aneurysms treated with clipping.[36,37] However, the study that showed a positive effect might not have matched the groups well enough for neurological condition on admission.[25] Another retrospective study on the administration of low-dose unfractionated heparin intravenously or subcutaneously to patients after clipping of the aneurysm showed a reduction in the occurrence of DCI in the patients who received the heparin intravenously.[35] One of the drawbacks of intravenous administration of unfractionated heparin is that it is prone to under- and overdosing, as it is monitored by the activated partial thromboplasty time (aPTT), which has a low sensitivity in critically ill patients.[38] Data on beneficial effects of different dosages of LMWH on the occurrence of DCI, especially after endovascular aneurysm treatment, are sparse, and therefore, the study described in **Chapter 7** was performed. In this study a benefit was found in aSAH patients with endovascularly treated aneurysms receiving high-dose Nadroparin (LMWH) (5700 IE, subcutaneously, twice daily) compared to patients receiving low-dose Nadroparine (2850 IE, subcutaneously, once daily), with regard to discharge-to-home and mortality rate. Patients receiving high-dose Nadroparin after coiling of the

aneurysm for the length of their hospital stay did show a lower incidence in the occurrence of DCI in this retrospective study. What exactly causes the beneficial effect on in-hospital mortality rate and discharge-to-home rate in patients receiving high-dose Nadroparin is not yet clear. And, although it is the largest study available in patients after endovascular cerebral aneurysm treatment, the results must be interpreted with caution, because of the retrospective nature of the study without standardized clinical and imaging follow-up.

Overall, the literature on the possible benefits of LMWH administration after aneurysm treatment in aSAH patients is sparse, especially after endovascular treatment. A randomized clinical trial to study the benefits of high-dose LMWH versus low-dose LMWH administration in these patients is currently being set up.

Future directions

Middle cerebral artery aneurysm treatment

Unruptured aneurysms

As there seems to be little difference in clinical and imaging outcome between conventional coiling and clipping in patients with unruptured MCA aneurysms, the most important questions for the individual patient are, and will be, whether treatment is mandatory, or not, and what the different risk profiles (e.g. rupture risk, morbidity, mortality) are of treatment versus no treatment, especially when a patient has no complaints and little or no risk factors. One important factor to discuss with such a patient, and which we did not address in our review, is the possible consequences on quality of life and neuropsychological functioning of treatment and no treatment. A recent review showed that treatment of unruptured aneurysms (in all locations) relieves the anxiety of having a cerebral aneurysm, and that there was no permanent decline in quality of life after treatment and no significant differences between coiling and clipping of aneurysms in all locations.[39] Regarding cognitive functioning, the authors state that "the effect of unruptured aneurysm treatment on cognition is domain-specific: there is a sparing of some domains (verbal fluency, cognitive flexibility, working memory, language, visuospatial ability, psychomotor ability) and a transient decline in others (verbal and visual memory)". Additionally, it is discussed whether the suboptimal employment rates of treated patients is caused by the treatment, or by the knowledge of having an aneurysm, or that it might even be attributed to other complaints, not related to the aneurysm. One drawback of this review is that most of the included studies were small (ranging from 15 to 72 patients) and single center studies and multiple different scoring systems were used. Improving the knowledge on the impact on quality of life of incidental MCA aneurysm treatment next to the understanding of the natural

course of aneurysm evolution in general, and the benefits and risks of different treatments, will help in finding the best treatment algorithm for the individual patient. While there are many scoring systems and tests to study quality of life and neuropsychological functioning (international) consensus must be reached on what are the best scoring systems or tests to be used in studies on incidental aneurysm treatment. These scores or tests can be used in future, large, prospective studies to be able to better inform the patients on the (possible) impact on daily life of incidental (MCA) aneurysm treatment.

Ruptured aneurysms

For ruptured aneurysms there is stronger evidence that for patients, meeting the inclusion criteria of the ISAT trial, there are benefits of coiling over clipping, with regard to clinical outcome and cognitive functioning.[1,13] To study patients with aneurysms who did not meet the inclusion criteria of the ISAT trial, the ISAT2 started including patients in 2013 and is still recruiting.[40] In this multicenter (the aim is 50 centers) study, the clinical outcome of patients with MCA aneurysms, who were relatively underrepresented in the ISAT trial, will be monitored separately. Additionally, patients who are treated with special surgical techniques, such as parent vessel occlusion and bypass surgery, and patients treated endovascularly with the use of additional devices, such as stents and flow diverters, will be included. This is in line with current EU regulations that state that new medical devices should be studied in randomized controlled trials (https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en, last accessed 08-02-2018). At this moment there is no evidence that treatment with additional endovascular devices leads to a better clinical outcome than surgical treatment. What we do know is that patients treated with those devices are bound to lifelong antiplatelet therapy. Hopefully, the ISAT 2 trial and future randomized controlled trials on the subject of additional endovascular devices will aid in selecting the best treatment for the individual patient with "regular" and more complex MCA aneurysms.

MCA aneurysms with a concomitant parenchymal hematoma

According to the results described in **Chapter 3** there is insufficient evidence for the statement in the American Heart Association guidelines for the management of aneurysmal subarachnoid hemorrhage that states that 'microsurgical clipping may receive increased consideration in patients presenting with large (more than 50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms'.[14] In addition, it is very difficult to define a certain intraparenchymal hematoma volume that would be eligible for clot removal. Therefore, it would be better to select a treatment algorithm based on the neurological condition on admission and the aneurysm configuration instead of on intraparenchymal hematoma volume. Most gain could possibly be

achieved in patients in poor neurological condition (GCS score < 8 and/ or abnormal pupil reactions) on admission and a space-occupying hematoma that is likely to be the cause of the poor neurological condition. This could be investigated in a multicenter study in which patients in poor neurological condition on admission are randomized for clot removal or not. The order in which the decompression, the aneurysm treatment and the clot removal are performed can be decided in a multidisciplinary team. To also be able to compare coiling and clipping in these patients the aneurysms must be eligible for both procedures, to be decided on the basis of the CTA made on admission, or the DSA with 3DRA, that can also be performed in a hybrid operation room. While the patients are in a poor neurological condition it would probably be the best to treat these patients as soon as possible. Treatment in a hybrid operation room is recommended to minimize the delay between decompression and a possible DSA or coiling of the aneurysm and to enable direct clot evacuation, when an aneurysm is endovascularly secured. Additionally, all data (demographic, imaging and treatment including complications) as described in the table on baseline characteristics in **Chapter 3** should be collected. The first postoperative imaging, if possible with a perfusion CT, must be performed directly (< 6 hours) after the treatment to enable its use as baseline imaging.[41] The short time interval after treatment is necessary to be able to differentiate possible treatment-related ischemia from edema and delayed cerebral ischemia during follow-up. Measuring clinical outcome with the modified Rankin scale score at fixed time intervals enables comparison between the treatment modalities of clinical outcome on discharge, and after three months and one year. With the results of such a study, firmer recommendations for a treatment algorithm in guidelines regarding the management of subarachnoid hemorrhage, such as the AHA guidelines, might be possible for patients with ruptured MCA aneurysms and a concomitant hematoma.

Automatic hemorrhage volume quantification

In **Chapter 4** the algorithm for automatic hemorrhage quantification on NCCT was successfully validated, and in **Chapters 5** and **6** we showed that the algorithm was successfully used in clinical studies on the association of hemorrhage volume after aSAH with the occurrence of DCI, but had some limitations. Currently, an AMC spin-off company (Nico-lab BV) is combining the current algorithm with machine learning techniques to try to improve its speed and usability. Machine learning is a general term for artificial intelligence that develops algorithms to enable computers to learn from existing data without explicit programming.[42,43] One possible way of machine learning is using convolutional neural networks (CNN), which is called deep learning. In the case of aSAH quantification on NCCT the data that are generated in **chapters 4**, **5** and **6** can be used to train convolutional neural networks. This is called supervised deep learning. These CNN's are able to automatically segment hemorrhage on NCCT. Whether this technique

is more accurate and faster than the technique described in **Chapter 4** and is able to segment hemorrhage on specific locations could be a topic for future studies. Currently, a study using CNN's for aSAH volume quantification is being performed in the AMC. A possible advantage of this deep learning technique is that there is no need for a separate workstation to extract the aSAH volume segmentation from a NCCT, because this can be automatically done at the level of the CT-scanner. If these segmentations are sent to a cloud they will be easily accessible for clinicians who have entry to the cloud. With these improvements, it will be possible for clinicians to visualize the quantified blood volume within minutes after CT image acquisition. This facilitates future research on the possible clinical implications of automatically quantified hemorrhage volume.

Hemorrhage volume is just one of the possible causes of DCI. Other possible causes of DCI must be better understood to be able to improve DCI prevention and treatment in general. Future research could focus on implementation of total hemorrhage volume and cisternal hemorrhage volume in a prediction model for DCI, with or without taking IVH into account. In such a study, it would be interesting to investigate whether accurately quantified hemorrhage volume has more value in prediction models than for instance the scores from the modified Rankin scale or the Barrow Neurological Institute scale. This can be done in a prospective patient cohort using a study design with decision tree analysis.[44,45]

Nadroparin and DCI

In **Chapter 7** we found a benefit in in-hospital mortality and return-to-home rates in aSAH patients receiving high-dose (5700 IE), subcutaneously administered, Nadroparin after coiling of the aneurysm as compared to patients receiving low-dose (2850 IE) Nadroparin. The administration was started after the coiling. Surprisingly, no benefit was found on the occurrence of DCI in these patients, but this study had some limitations, mainly because of the retrospective nature of the data and the suboptimal clinical and imaging follow-up. To make a stronger statement on the possible clinical benefits (e.g. DCI occurrence and outcome) and potential drawbacks (e.g. bleeding) of high-dose versus low-dose Nadroparin administration after endovascular aSAH treatment, a prospective, randomized trial is needed. In this trial the imaging and clinical follow-up will be standardized and the baseline characteristics including neurological condition on admission equal in both groups. The duration of treatment will be standardized. Currently, a randomized controlled trial protocol is being processed.

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Appendix.

Summary

In this thesis different aspects of aneurysmal subarachnoid hemorrhage (aSAH) are investigated with an emphasis on middle cerebral artery (MCA) aneurysm treatment outcome, hemorrhage volume quantification on different locations, and delayed cerebral ischemia (DCI). First, the literature is reviewed to study the clinical and imaging outcome of clipping and coiling of MCA aneurysms. Next, the association of intraparenchymal hematoma volume (≤/> 50ml) after aSAH of MCA aneurysms with clinical outcome is studied. Furthermore, a new automatic hematoma quantification method is validated in a cohort of patients with MCA aneurysms. This method is used in two studies to investigate the association of hematoma volume (total and location-specific) with the occurrence of DCI in patients with aneurysms on various locations. Lastly, the difference in the occurrence of DCI and in clinical outcome of patients with endovascularly treated aneurysms receiving either high- or low-dose nadroparin after the treatment is studied.

In **Chapter 2** we describe a systematic literature review to assess the clinical and imaging outcome of clipping and coiling of (un)ruptured MCA aneurysms. Fifty-one studies were included in the analysis. We found that both coiling and clipping are procedures with low mortality and morbidity rates and, although it may have seemed that coiling was better for ruptured aneurysms and clipping for unruptured aneurysms, no firm conclusions could be drawn due to the variation in study design and the lack of standardized reporting on MCA aneurysm treatments. A multidisciplinary approach in large volume neurovascular centers is therefore recommended with selection of the optimal treatment modality, based on the clinical condition of the patient and the morphological aspects of the aneurysm.

Chapter 3 challenges a AHA guideline by describing a patient cohort of 81 patients admitted with ruptured MCA aneurysms and concomitant intraparenchymal hematomas. Clinical outcome data were available for 76 patients. A significant difference in favorable outcome (17% versus 68%) was seen when comparing patients with poor and good neurological condition on admission ($p < 0.01$). Patients with hematomas > 50 ml had similar outcomes for coiling and clipping, all underwent decompression. Patients with hematomas < 50 ml did not show differences in favorable outcome when comparing coiling and clipping, with (33% and 31%, respectively) or without decompression (90 and 88%, respectively). Therefore, even in patients with large hematomas, the neurological condition on admission and the aneurysm configuration seem to be equally important factors to determine the most appropriate treatment strategy.

In **Chapter 4** we validated an automatic hemorrhage volume and density quantification method by comparing them to manual delineation (by two radiologists) on NCCT images in a cohort

of 30 patients with ruptured MCA aneurysms. We found that automatic volume and density quantification was very accurate compared to manual assessment.

Chapter 5 describes a cohort of 333 patients suffering from aSAH admitted to two academic hospitals. The total hemorrhage volume after aSAH on NCCT was quantified with the automatic quantification method described in Chapter 4. We found that a higher total hemorrhage volume after aSAH, measured with our automated quantification method on NCCT, was significantly (Odds ratio (OR) 1.02 per ml, 95% CI 1.01–1.03) associated with the occurrence of DCI. The presence of an intraventricular hemorrhage was also significantly (OR 2.66, 95% CI 1.37–5.17) associated with the occurrence of DCI.

In **Chapter 6** we investigated the association of hemorrhage volume at different locations (subdural, cisternal, intraparenchymal and intraventricular) with occurrence of DCI. Only the cisternal hemorrhage volume was significantly (OR 1.02 per ml, 95% CI 1.01–1.04) associated with the occurrence of DCI. Whereas the presence of intraventricular hemorrhage was significantly associated with the occurrence of DCI, the intraventricular hemorrhage volume in milliliters was not.

Chapter 7 describes a cohort of 158 patients with endovascularly treated patients after aSAH. Ninety-three patients had received high-dose Nadroparin, and 65 patients prophylactic low-dose Nadroparin after coiling of the aneurysm. There was no significant difference in the occurrence of clinical DCI between patients treated with high-dose (34%) and low-dose (31%) Nadroparin. More patients were discharged to home after receiving high-dose Nadroparin (40%) compared to low-dose Nadroparin (17%) (OR 3.13, 95% CI 1.36–7.24). Furthermore, mortality was lower in the high-dose group (5%) compared to the low-dose group (23%) (OR 0.19, 95% CI 0.07–0.55), also after adjusting for neurological status on admission (OR 0.21, 95% CI 0.07–0.63). A randomized controlled trial is currently being set up.

Samenvatting

In dit proefschrift worden verschillende aspecten van aneurysmatische subarachnoïdale bloedingen (aSAB) onderzocht, waarbij de nadruk ligt op de klinische uitkomst van patiënten met een arteria cerebri media (ACM) aneurysma, kwantificatie van bloedingsvolumes op verschillende intracerebrale locaties, en delayed cerebral ischemia (DCI). Als eerste is de literatuur bestudeerd om het klinische resultaat en het resultaat op beeldvorming van het coilen en clippen van ACM aneurysmata te onderzoeken. Vervolgens is de associatie tussen het intraparenchymateuze hematoomvolume (≤/> 50 ml) na een subarachnoïdale bloeding als gevolg van een aneurysma en de klinische uitkomst onderzocht. In de volgende studie werd een nieuwe methode voor automatische kwantificatie van het bloedingsvolume gevalideerd in een cohort van patiënten met een ACM aneurysma. Deze methode werd vervolgens toegepast in twee studies om de associatie tussen het bloedingsvolume (totaal en op verschillende locaties) met het ontstaan van DCI te onderzoeken. Tot slot werd onderzocht of er een verschil in klinische uitkomst en in het ontstaan van DCI bestond tussen patiënten die na endovasculaire behandeling van hun aneurysma behandeld werden met een hoge of lage dosis Nadroparine.

In **Hoofdstuk 2** beschrijven we een systematische review van de literatuur om de klinische uitkomst en de uitkomst op beeldvorming te onderzoeken van patiënten met een (on) geruptureerd ACM aneurysma. Eenenvijftig studies werden geïncludeerd voor de analyses. We vonden dat coilen en clippen beide procedures zijn met lage mortaliteit en morbiditeit percentages. Ondanks dat het leek of coilen beter was voor geruptureerde aneurysmata en clippen voor ongeruptureerde aneurysmata, konden we geen harde conclusies trekken als gevolg van de variatie in studieopzet en het ontbreken van gestandaardiseerde verslaglegging van de behandeling van ACM aneurysmata. Het is aan te raden om deze patiënten te behandelen in grote neurovasculaire centra, waarbij in een multidisciplinaire setting de beste behandeling wordt bepaald, gebaseerd op de klinische conditie en de morfologische aspecten van het aneurysma.

In **Hoofdstuk 3** wordt de AHA richtlijn uitgedaagd door het beschrijven van 81 patiënten die opgenomen waren met een ACM aneurysma en een bijkomend intraparenchymateus hematoom (IPH). De klinische uitkomstdata waren bekend van 76 van deze patiënten. We vonden een significant verschil in gunstige klinische uitkomst (17% versus 68%) tussen patiënten die bij opname in een goede en een slechte neurologische conditie waren ($p < 0.01$). Patiënten met hematomen van meer dan 50 ml hadden een vergelijkbare klinische uitkomst na coilen en clippen. Al deze patiënten werden behandeld met decompressie. Analyses van patiënten met hematomen kleiner of gelijk aan 50 ml lieten geen verschil in gunstige klinische uitkomst zien bij de vergelijking tussen coilen en clippen met (respectievelijk 33% en 31%) of zonder decompressie (respectievelijk 90% en 88%). Derhalve lijken, zelfs bij patiënten met grote

hematomen, de neurologische conditie bij opname en de configuratie van het aneurysma even belangrijke factoren bij het bepalen van de meest geschikte behandelstrategie.

In **Hoofdstuk 4** hebben we een methode voor automatische kwantificatie van bloedingsvolume en -densiteit gevalideerd door de metingen te vergelijken met manuele metingen (verricht door twee radiologen) op blanco CT beelden in een cohort met 30 patiënten met een geruptureerd ACM aneurysma. We vonden dat automatische volume en densiteit kwantificatie zeer accuraat was in vergelijking met de manuele metingen.

Hoofdstuk 5 beschrijft een cohort van 333 patiënten die opgenomen waren met een aSAB in twee verschillende academische centra. Het totale bloedingsvolume na de aSAB werd gekwantificeerd op blanco CT beelden met de kwantificatiemethode beschreven in hoofdstuk 4. We vonden een significante (Odds ratio (OR) 1.02 per ml, 95% CI 1.01–1.03) associatie tussen een hoger totaal bloedingsvolume na aSAB, gemeten op blanco CT beelden met de automatische kwantificatiemethode, en het ontstaan van DCI. We vonden ook een significante (OR 2.66, 95% CI 1.37–5.17) associatie tussen de aanwezigheid van een intraventriculaire bloeding en het ontstaan van DCI.

In **Hoofdstuk 6** hebben we de associatie tussen het bloedingsvolume op verschillende locaties (subduraal, cisternaal, intraparenchymateus en intraventriculair) en het ontstaan van DCI onderzocht. Alleen het cisternale bloedingsvolume had een significante (OR 1.02 per ml, 95% CI 1.01–1.04) associatie met het ontstaan van DCI. Alhoewel de aanwezigheid van een intraventriculaire bloedingscomponent een significante associatie had met het ontstaan van DCI, had het intraventriculaire bloedingsvolume in milliliters dit niet.

Hoofdstuk 7 beschrijft een cohort van 158 patiënten met een aSAB waarvan het aneurysma endovasculair behandeld werd. Drieënnegentig patiënten kregen een hoge dosis Nadroparine, en 65 patiënten een profylactische dosis Nadroparine na het coilen van het aneurysma. Er was geen significant verschil in het ontstaan van DCI tussen patiënten die behandeld werden met een hoge dosis (34%) en een profylactische dosis (31%) Nadroparine. Meer patiënten (40%) die de hoge dosis Nadroparine kregen, werden naar huis ontslagen in vergelijking met patiënten (17%) (OR 3.13, 95% CI 1.36–7.24) die de profylactische dosis Nadroparine kregen. Bovendien was de mortaliteit in de hoge dosis groep (5%) lager dan in de groep (23%) (OR 0.19, 95% CI 0.07–0.55) die de profylactische dosis kreeg, ook als er rekening gehouden werd met een mogelijk verschil in neurologische status bij opname (OR 0.21, 95% CI 0.07–0.63). Een gerandomiseerd vergelijkend onderzoek wordt op dit moment voorbereid.

In **Hoofdstuk 8** worden de hoofdstukken twee tot en met zeven bediscussieerd en worden mogelijke verbeteringen voor de toekomst besproken.

List of abbreviations

CI	Confidence interval
CNN	Convolutional neural network
CT(A)	Computed tomography (angiography)
CSF	Cerebrospinal fluid
DCI	Delayed cerebral ischemia
DSA	Digital subtraction angiography
EVD	External ventricular drain
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
GM	Gray matter
HH	Hunt & Hess score
HU	Hounsfield units
ICC	Intraclass correlation coefficient
ICH	Intracerebral hemorrhage
IPH	Intraparenchymal hematoma
IQR	Interquartile range
IVH	Intraventricular hematoma
(U)LMWH	(Ultra)Low-molecular-weight heparin
LPBA40	Laboratory of neuro imaging probabilistic brain atlas
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
mRS	Modified Rankin scale
NCCT	Non-contrast computed tomography
NOS	Newcastle-Ottawa quality assessment Scale for cohort studies
(a)OR	(adjusted) Odds ratio
(a)SAH	(aneurysmal) subarachnoid hemorrhage
SD	Standard deviation
SDH	Subdural hematoma
TBV	Total blood volume
WFNS scale	World Federation of Neurosurgical Societies subarachnoid hemorrhage grading scale
WM	White matter

Grading scales

GLASGOW COMA SCALE

Patient Name: _____
Rater Name: _____
Date: _____

Activity		Score
EYE OPENING		
None	1 = Even to supra-orbital pressure	
To pain	2 = Pain from sternum/limb/supra-orbital pressure	
To speech	3 = Non-specific response, not necessarily to command	
Spontaneous	4 = Eyes open, not necessarily aware	_____
MOTOR RESPONSE		
None	1 = To any pain; limbs remain flaccid	
Extension	2 = Shoulder adducted and shoulder and forearm internally rotated	
Flexor response	3 = Withdrawal response or assumption of hemiplegic posture	
Withdrawal	4 = Arm withdraws to pain, shoulder abducts	
Localizes pain	5 = Arm attempts to remove supra-orbital/chest pressure	
Obeys commands	6 = Follows simple commands	_____
VERBAL RESPONSE		
None	1 = No verbalization of any type	
Incomprehensible	2 = Moans/groans, no speech	
Inappropriate	3 = Intelligible, no sustained sentences	
Confused	4 = Converses but confused, disoriented	
Oriented	5 = Converses and oriented	_____

TOTAL (3–15): _____

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Teasdale G, Jennett B. "Assessment of coma and impaired consciousness. A practical scale." *The Lancet* 13;2(7872):81-4, 1974.

GLASGOW OUTCOME SCALE

Patient Name: _____
Rater Name: _____
Date: _____

Note: The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no *obvious cortical* function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

TOTAL (1–5): _____

References

Jennett B, Bond M. "Assessment of outcome after severe brain damage."
Lancet 1975 Mar 1;1(7905):480-4

HUNT & HESS SCALE

Patient Name: _____
Rater Name: _____
Date: _____

For non-traumatic sub-arachnoid hemorrhage patients.

(Choose single most appropriate grade.)

Description	Grade
Asymptomatic, mild headache, slight nuchal rigidity	**1**
Moderate to severe headache, nuchal rigidity , no neurologic deficit other than cranial nerve palsy	**2**
Drowsiness / confusion, mild focal neurologic deficit	**3**
Stupor, moderate-severe hemiparesis	**4**
Coma, decerebrate posturing	**5**

GRADE (1–5): _____

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Hunt WE, Hess RM. "Surgical risk as related to time of intervention in the repair of intracranial aneurysms." *Journal of Neurosurgery* 1968 Jan;28(1):14-20.

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MODIFIED RANKIN SCALE (MRS)

Patient Name: _____
Rater Name: _____
Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

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***Stroke* 1988 Dec;19(12):1497-1500**

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. "Interobserver agreement for the assessment of handicap in stroke patients."
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World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage - (WFNS) scale

Overview :

The clinical grading system proposed by the World Federation of Neurologic Surgeons is intended to be a simple, reliable and clinically valid way to grade a patient with subarachnoid hemorrhage. This system offers less interobserver variability than some of the earlier classification systems.

Glasgow Coma Score	Motor Deficit	Grade
15	absent	1
13 - 14	absent	2
13 - 14	present	3
7 - 12	present or absent	4
3 - 6	present or absent	5

*Where a motor deficit refers to a major focal deficit.

Interpretation:
• Maximum score of 15 has the best prognosis
• Minimum score of 3 has the worst prognosis
• Scores of 8 or above have a good chance for recovery
• Scores of 3-5 are potentially fatal, especially if accompanied by fixed pupils or absent oculovestibular responses
• Young children may be nonverbal, requiring a modification of the coma scale for evaluation

In assessing outcome of subarachnoid hemorrhage, the Federation recommended use of the Glasgow Coma Scale:

Glasgow coma scale = (score for eye opening) + (score for best verbal response) + (score for best motor response)

Eye Opening	Score
Spontaneously	4
To verbal stimuli	3
To pain	2
Never	1

Best Verbal Response	Score
Oriented and converses	5
Disoriented and converses	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

Best Motor Response	Score
Obeys commands	6
Localizes pain	5
Flexion withdrawl	4
Abnormal flexion (discorticate rigidity)	3
Extension (decerebrate rigidity)	2
No response	1

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lachend terugkijken op deze soms onmogelijke periode met onze drukke banen, diensten, zwangerschappen, de verbouwing, de verhuizing naar Bussum en het chronische gebrek aan nachtrust. Dat we dit samen zo goed doorstaan, geeft veel vertrouwen voor de toekomst. Dikke kus voor mijn lieve, mooie, sterke dushi!

About the author

IJsbrand Zijlstra was born on Februrary 10th 1980 in Helmond, the Netherlands. In Helmond he lived together with his older brother Rintse, his older sister Anne- Linde, his twin brother Steven, his parents Jan and Vera and their black Labrador Bess. In 1998 he graduated from the Carolus Borromeus College in Helmond having followed eight classes including Latin language. In this year he started medical school at the university of Groningen. In 2003 he joined a research project of Prof. Tjip van der Werf (university of Groningen) to study Buruli ulcers' disease in Dunkwa on Offin, Ghana for six months. This resulted in his first publication and together with the research results of other students, international researchers and local doctors this resulted in a multimillion dollar fund from the World Health Organization for further research on this disease. In the second half of 2003 and the first half of 2004 he followed internships at the St Elisabeth hospital on the isle of Curacao. During that year he participated in the Pan American field hockey cup in Ontario (Canada) representing the Netherlands Antilles, and, more importantly, he met his wife Annelieke. Near the end of his regular internships at the Groningen university hospital in 2005 he applied for his final internship interventional radiology at the Academic medical center (AMC) in Amsterdam and was accepted. They advised him to work for one year as a surgery resident and so he did at the Bovenij hospital in Amsterdam. In September 2006 he started his residency at the radiology department of the AMC. After his general radiology residency he completed a fellowship in interventional radiology at the AMC in Amsterdam in September 2012 and passed the exam of the European board of interventional radiology (EBIR). This is when he started working on his PhD under supervision of Prof. Dr. Charles Majoie and Dr. Rene van den Berg. Dr. Dagmar Verbaan and Prof. Dr. Peter Vandertop later on completed the team. The research first focused on middle cerebral artery aneurysm treatment and later on also on hematoma volume quantification and delayed cerebral ischemia. During the years of his PhD candidacy he married his wife Annelieke. Together they travelled around the world in 2014/15 and ran the New York marathon in 2015. In September 2016 their son Taeke was born and in January 2018 their daughter Guusje. In the three weeks after her birth this thesis was finalized. Currently, IJsbrand is working as an interventional radiologist in the AMC (which in 2018 was renamed Amsterdam UMC, location AMC) in Amsterdam.