EARLYDRAIN - Study Protocol

Stefan Wolf, Jürgen Bardutzky, Peter Vajkoczy, Stefan Schwab

Version 1.3

January, 3rd, 2010

Objective:

To investigate whether early application of a lumbar drainage improves clinical outcome after aneurysmal subarachnoid hemorrhage.

Background:

Patients suffering from aneurysmal subarachnoid hemorrhage (SAH) are predominantly threatened by two distinct medical problems. Firstly, they may experience a second – and often more severe – hemorrhage, and secondly, they may suffer a constringency reaction of the vessels supplying the brain with blood, called vasospasm.

The first problem is resolved by rapid cerebrovascular imaging and subsequent treatment of the ruptured aneurysm, thus preventing recurrent hemorrhage. Aneurysm treatment may be performed either via craniotomy and surgical clipping of the aneurysm or with endovascular techniques by occluding the aneurysm with small platinum coils.

The vasospasm - the second problem - is more difficult to handle. The incidence of symptomatic vasospasm is about 30 to 60% after aneurysmal SAH, depending on definition (1). The sequelae of cerebral vasospasm are permanent neurologic deficits, including death, due to infarction of the brain. Clinical signs of vasospasm include neurologic decline, hemipareses or any other focal neurologic deficit not explained by other reasons like posthemorrhagic hydrocephalus or electrolyte imbalances. The pathomechanism leading to vasospastic vessel constriction is incompletely understood (2). Diagnostic procedure of choice

is the digital subtraction angiography. Vasospasm may be present in the proximal vessels, the distal branches of the vasculature or both.

Prophylactic application of the calcium channel blocker nimodipine is currently the only therapy recognized for prevention of vasospasm (3). Newer approaches currently not included in official guidelines but performed in several centers are medication with statins and magnesium (4).

A hypothesis is that the development of vasospasm is related to the amount of blood in the basal cisterns. Therefore, a possible strategy tries to remove this blood as much as possible. If the aneurysm leading to the initial hemorrhage is secured via surgical therapy, some surgeons prefer to open the terminal lamina and irrigate the blood from the basal cisterns. Albeit promising, studies addressing this approach show mixed results (5). Opening of the basal cisterns and irrigation of the blood is not feasible if the aneurysm is secured with endovascular techniques.

Excess removal of cerebral spinal fluid (CSF) via an external ventricular drain fails in preventing vasospasm and may lead to a higher incidence of posthemorrhagic shunt dependency (6; 7). Reason is that after aneurysmal SAH, the blood is packed more densely in the basal cisterns and therefore only CSF, being more lightweight, is drained from the ventricles. As an alternative approach, application of a lumbar drain is proposed to address clotting of the blood in the basal cisterns. Three retrospective studies in patients after aneurysmal SAH, the newest being available only as abstract, were able to establish the safety of this approach (8-10). One of the fully published studies addressed vasospasm prophylaxis after surgical clipping (8), while the other was performed in patients after endovascular coiling (9). All studies led to a markedly diminished incidence of angiographic vasospasm. Therefore, a prospective study addressing the efficacy of this novel therapeutic approach is warranted.

The focus of the EARLYDRAIN study is to examine the efficacy of application of lumbar drainage in patients with acute subarachnoidal hemorrhage from a cerebral aneurysm. Hypothesis is that early application of lumbar drainage after aneurysmal SAH leads to a diminished incidence of cerebral vasospasm, as assessed by digital subtraction angiography, and an improved outcome, measured by the modified Rankin score, at six months.

Study outline

Patients suffering from aneurysmal SAH are treated according to international guidelines. Aneurysm treatment is at the discretion of the neurovascular team taking care for a patient and not specified by the study protocol. All medical treatment is performed according to local guidelines.

Any patient meeting the inclusion criteria and not violating the exlusion criteria may participate in the EARLYDRAIN study and randomized to either receive a lumbar drain or not, thus defining the two distinct groups LD and NoLD. To prevent premature rupture of the aneurysm due to accidental drainage, randomization to the study and eventual placement of a lumbar drain takes place after securing the aneurysm by the preferred method of choice. Any patient in the LD group receives a lumbar drain during anesthesia required for aneurysm treatment. This is to be performed prior to the start of anticoagulation or antiplatelet therapy is initiated, which sometimes is warranted after endovascular coiling. A postprocedural CCT scan of the brain is performed within to 24 hours of aneurysm treatment. In case of any neurological worsening after the procedure or clinical suspicion of threatening herniation, it is strongly recommended to advance the postprocedural CCT scan before commencing CSF diversion via the lumbar drain.

In patients in the LD group, after insertion of the drain CSF is drained slowly and steadily at a rate of approximately 5 ml per hour. This leads to a planned daily CSF drainage of about 120 ml per day via lumbar route. Patients in both groups group may receive additional CSF

drainage via a ventricular device as required. The amount of CSF drained via ventricular route is according to clinical requirement and not specified.

To facilitate accuracy of drainage, regular drainage control every other hour and stopping in case of unwarranted excess drainage is strongly recommended by the principal investigators. In case of neurological decline suspiciously related to the lumbar drainage, the drain is closed immediately and may be gradually restarted after 12 to 24 hours, after performing a CCT scan.

In patients requiring sedation and mechanical ventilation, either due to neurological impairment or otherwise, intracranial pressure monitoring is mandatory. This may be performed according to local policy either with parenchymal or ventricular devices. If the intracranial pressure exceeds 20 mmHg, further CSF drainage via lumbar route shall be interrupted until the ICP is below 20 mmHg again. Commencing carefully CSF drainage via the lumbar route may be still warranted in case of high intracranial pressure (11), but is at the discretion of the local investigator.

Further neuromonitoring with TCD, EEG, brain tissue oxygenation, jugular bulb oxymetry, regional cerebral blood flow, microdialysis or other devices is at the discretion of the center and according to its local guidelines. As far as possible, this data should be saved electronically for post-hoc analysis.

A CCT scan as well as conventional digital subtraction angiography for assessment of angiographic vasospasm is routinely performed on day 7 to 10 after the initial hemorrhage, regardless of the patient condition. In case of clinical suspicion of vasospasm, angiography may be performed at any time. If it is performed earlier and the patient shows no clinical deterioration thereafter, the angiography on day 7 to 10 is omitted.

After the control angiography on day 7 to 10, or day 8 in case of an earlier angiography, the lumbar drainage of CSF is stopped in the LD group. It may be pursued on a clinical base, as required.

Amount and duration of CSF drainage

Patients randomized to the lumbar drainage group shall receive a daily drainage of 120 ml CSF, or 5 ml per hour for seven days. If higher amounts of CSF need to be drained on clinical grounds as in patients with hydrocephalus, this is preferably performed via external ventricular drain.

The drain is planned to remain in place until the control angiography on day 7 to 10 after the initial hemorrhage. The local investigator may decide to remove the drain earlier in patients fully mobilized without clinical necessity of CSF drainage. However, consecutive drainage should not be go below four days to achieve a valid study result. Lumbar CSF drainage may be prolonged beyond the control angiography on clinical requirement. The amount of CSF drainage may then be adjusted to clinical needs and bears no further restriction.

Patients randomized to the control group should not receive a lumbar drain before the planned control angiography to be performed on day 7 to 10 after SAH. If the patient develops hydrocephalus, and no EVD was placed initially for CSF drainage, a lumbar drain may be installed at the discretion of the local investigator. These patients are analyzed in the intention-to-treat analysis, but are not suitable for per-protocol analysis.

Study in- and exclusion criteria

Inclusion criteria:

- Age of 18 years or older
- First aneurysmal SAH
- Pre-morbid modified Rankin Scale score 0 or 1
- Aneurysm treatment performed in the first 48 hours after the initial hemorrhage.
- Informed consent by the patient or his/her legal representative. In case neither the patient is capable of giving informed consent nor a legal representative is available,

informed consent can be given by an independent physician neither involved in the patient´s treatment nor the trial (for specification see below)

Exclusion criteria:

- Subarachnoid hemorrhage of other than aneurysmal origin
- No hemorrhage visible on initial CCT scan (Fisher Grade I)
- Pregnancy
- Concurrent participation in another interventional trial (participation in an observational trial is allowed)
- Life expectancy less than 1 year for other reasons than the actual SAH
- Other concomitant severe disease that would confound with treatment
- Other clear contraindication for treatment

Consent to the study

Consent for study inclusion is sought after explanation and agreement to a specific treatment. Thus, patients capable of consenting to the aneurysm treatment get the study details explained themselves and may or may not agree to participate. If a patient is incapable for consenting to the proposed treatment, the legal representative should be informed on the conditions of treatment choices and afterwards, on the details of the EARLYDRAIN study. A patient may be randomized if the legal representative gives informed consent to the study, based on the presumed will of the patient. If neither the patient is capable of giving informed consent nor a legal representative is available in due time, an independent physician not involved in the patient´s treatment nor in the trial may be asked for study approval. In either case of a patient being not capable of consenting himself, a legal representative needs to be established as soon as possible, according to German law. As soon as a legal representative is available and/or the patient has regained informed consent he/she must be asked to give informed consent. In the case where informed consent is not given after inclucion of a patient by an independent

physician, the patient or his/her legal representative are asked to give consent for evaluation of already acquired data.

Safety of lumbar drains after aneurysmal SAH

In all three retrospective studies, mortality was lower in the lumbar drainage group. None of the retrospective studies mentions procedural related complications for the lumbar drains (8-10). In patients with increased intracranial pressure, careful lumbar drainage of CSF may facilitate treatment even in case of compressed basal cisterns (11). To date, there is no data available indicating an increased risk of lumbar drainage in a controlled neurointensive care environment.

Insurance coverage

As the EARLYDRAIN study compares two standard procodures of CSF drainage after subarachnoid hemorrhage used in clinical routine, no additional patient insurance is necessary to perform the study. German laws §§ 40 to 42 Arzneimittelgesetz or §§ 20 to 23 Medizinproduktegesetz are not applicable. Any hypothetical adverse events of either treatment are covered by the regular treatment contracts which do include clinical research. This is to be confirmed by the Ethics committee as well as an informatory inquiry at an company specializing in trial insurance.

Outcome assessment:

The primary endpoint is disability after 6 months, assessed by the modified Rankin Scale (12; 13), dichotomized at a score of 0 to 2 versus 3 to 6 (6=death). Assessment is performed by a blinded investigator of the local study center by personal visit. Alternatively, a telephone questionnaire is suitable for outcome assessment of the modified Rankin Scale (13). Outcome assessment is planned to be done on the whole dataset as well as in preplanned stratified subsets (i.e. for example clinical SAH grade according to the Hunt&Hess scale 1-2 vs. 3-5 (14), CT grading according to Fisher I-III vs. IV (15)).

Secondary outcome criteria include:

- Mortality after 6 months
- mRS score after 6 months as continuous variable
- Angiographically vasospasm at day 7 to 9, as defined by a caliber reduction by 33% or more compared to the initial digital subtraction angiography
- Vasospastic infarction in the last CT scan before discharge
- Expression of clinical delayed neurological deficit in the first 14 days after the aSAH.
- Daily course of TCD mean flow velocity in both MCA at a depth of 50-60 mm
- Rate of death during the initial hospital treatment after the aSAH.
- Rate of CSF shunt insertion in the first six months
- Presence of CSF infection during the first 14 days, as defined by modified CDC criteria for device-associated meningitis (treatment required on either positive culture, or elevated cell count, red cell/ white cell ratio, increased lactate and/or decreased glucose). (16)

The following parameters will be recorded and used in predictor-/association models concerning primary and/or secondary outcome parameters:

- Gender
- Age
- Hunt&Hess Scale on admission
- Time from symptom onset to admission
- Localisation of aneurysm
- Time from symptom onset to aneurysm treatment
- Treatment of aneurysm by clipping or coiling or both
- Time from symptom onset to randomization

- Time from symptom onset to treatment start (i.e. insertion of the lumbar drainage in the treatment arm)
- Time from admission to discharge
- Insertion of EVD (yes/no)
- Duration of EVD
- Duration of lumbar drainage
- Amount of CSF drainage drained by EVD (ml)
- Amount of CSF drainage drained by lumbar drainage (ml)
- Use of Nimodipine (yes/no)
- Use of statins (yes/no)
- Use of Mg^{2+} (yes/no)
- Transcranial Doppler ultrasound, 1x daily (>160 cm/s versus <160 cm/s)
- Presence of CSF infection during hospital stay (yes/no)

Serious adverse events (SAE)

Adverse events, risks

Every patient is treated according to international guidelines. 50% of patients are additionally treated by lumbar drainage.

Surgery-related complications: Surgical treatment includes the known risks of surgical interventions:

Definition of adverse events and severe adverse events

The term „adverse event“ (AE) describes any sign, symptom, syndrome or any disease 1. occurring newly in a trial participant after consent to the trial and 2. being of particular interest for the assessment of the disease or the security of the therapeutic concept. In this trial AEs include:

- arterial or venous thromboses,

- complications related to insertion of a lumbar drainage,
- any SAE

The term AE does not implicate a causal correlation with the participation in the trial. Surgical interventions are not necessarily considered as AE but can be necessary for the therapy of an AE. AEs are divided in severe (SAE) and not severe (AE) adverse events. A SAE is any AE occurring during the trial that is related to:

- death
- any live-threatening condition,
- re-hospitalisation or prologation of hospitalisiation,
- long-term or severe restraint of the state of health, or
- birth deformities.

Documentation

Investigation of AEs is part of every visit and any AE has do be documented in the CRF.
Every SAE has to be documented on a special documentation form and has to be reported within 24 hours after recording, but at least at the next working day, to the co-ordinating study center:

Address: Dr. Stefan Wolf
Charité-Universitätsmedizin Berlin
Neurochrurgische Klinik
Augustenburger Platz 1
13353 Berlin
Tel.: 030-450-560-
Fax: 030-450-560-
Email: stefan.wolf@charite.de

The responsible investigator at the study center in Berlin has to inform the monitor of the trial (CSB) as soon as possible. SAEs are reported to the ethics committee according to local standards. The Data Safety and Monitoring Board (DSMB) has to be informed about SAEs at least every 6 months (if necessary earlier), starting with the day of inclusion of the first patient. The responsible study center has to pursue further changes and outcomes of SAEs, regarding intensity and potential relations to treatment. Evaluation of SAEs is performed by CSB.

Emergency

The occurance of a SAE does not automatically implicate a preliminary stop of the patient's participation in the trial, but requires immediate initiation of diagnostic and therapeutical measures for the protection of the patient's health.

Principal investigators:

Stefan Wolf, M.D.

Department of Neurosurgery, Charite Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

stefan.wolf@charite.de

and

Jürgen Bardutzky, M.D., Ph.D., Department of Neurology, Friedrich-Alexander University Erlangen, Schwabachanlage 6, 91054 Erlangen, Germany

Juergen.Bardutzky@uk-erlangen.de

Study sites:

Study sites to participate in the EARLYDRAIN trial should treat at least 30 patients with aneurysmal subarachnoid hemorrhage per year. Preferrably, to decrease the variability between centers and ensure adequate recruitment frequency, a maximum of 8 to 10 centers is warranted.

Promotion of the EARLYDRAIN study is performed at the next national meetings of the German and international societies of Neurology and Neurosurgery as well as direct propagation.

Ethic approval:

Each participating center seeks for its own ethic approval. The ethic vote from the principal investigators should be provided.

Trial registration

After approval by the ethics committee at the site of the main investigators, the trial protocol will be registered at www.clinicaltrials.gov.

Study size planning

In the ISAT trial, the largest trial on the treatment of aneurysmal subarachnoid hemorrhage so far, the mortality at one year follow-op was about 8.1% to 10.1% (17). Given the data from both fully published studies on lumbar drains after SAH, a reduction from 15% to 2.1% after coiling and from 5% to 3 % after clipping was shown. Thus, both studies were way lower in their mortality rate and, therefore, their external validity may be questioned.

In the three retrospective trials, 167, 107 and 79 patients were studied. The effect of LD was a decrease in the incidence of vasospasm by 34%, 40% and 54%, respectively. However, the definition of endpoints was not equal in the retrospective studies.

To assess a decrease of the incidence of clinical vasospasm from 40% to 20% in a prospective clinical trial, 93 patients in each of the two study arms are required to gain a power of 85%, using an alpha error of 5%. To account for possible imbalances in the randomization procedure concerning severity of clinical and radiological grading of the SAH or the choice of treatment and to facilitate a preplanned analysis on the severity of the initial hemorrhage, the planned study size is to include and randomize altogether 216 patients. These calculations are done according the following assumptions:

Two Independent Proportions (Non-Null Case) Power Analysis

Numeric Results of Tests Based on the Difference: P1 - P2
H0: P1-P2=D0. H1: P1-P2=D1<>D0. Test Statistic: Z test (unpooled)

Power	Sample Size Grp 1 N1	Sample Size Grp 2 N2	Prop Grp 2 or Control P2	Prop|H0 Grp 1 or Trtmnt P1.0	Prop|H1 Grp 1 or Trtmnt P1.1	Diff if H0 D0	Diff if H1 D1	Target Alpha	Actual Alpha	Beta
0.9008	108	108	0.8000	0.7000	0.5000	-0.1000	-0.3000	0.0500		0.0992
0.9007	71	71	0.8000	0.7500	0.5000	-0.0500	-0.3000	0.0500	0.0545	0.0993
0.9003	50	50	0.8000	0.8000	0.5000	0.0000	-0.3000	0.0500	0.0575	0.0997

Note: exact results based on the binomial were only calculated when both N1 and N2 were less than 100. Group sample sizes of 108 in group one and 108 in group two achieve 90% power to detect a

difference between the group proportions of -0.3000. The group two proportion is 0.8000. The group one proportion is assumed to be 0.7000 under the null hypothesis and 0.5000 under the alternative hypothesis. The test statistic used is the two-sided Z test (unpooled). The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design is NA.

This is consistent with the effect size from the retrospective trials (8-10).

The EARLYDRAIN investigators are aware of other, more conservative calculations for the sample size of vasospasm studies, indicating there may be the necessity to include more than 5000 patients in a single trial (18). The power calculations, as described above and based on the available retrospective data, do not substantiate numbers this large. Besides feasibility issues, clinical experience from the principal investigators considering the expected effort-benefit ratio does not warrant enlargement of the trial to detect a rather small difference between groups.

Statistical Analysis

All data are described according to their mean, median or frequency, as applicable. The dichotomized modified Rankin score as target outcome variable is investigated univariately against treatment group. Multivariate logistic regression modeling is performed accordingly, adjusted for clinical grade, fisher grade, ventricular hemorrhage, parenchymal hemorrhage, gender, nimodipine or other concomitant medical treatment. Analysis is planned as intention-to-treat as well as per protocol, excluding the patients who were treated with amounts of CSF drainage via lumbar drain deviating from the specified 5 ml/h or which needed a lumbar drain when randomized to the No-LD group.

Interim Analysis

An interim analysis after inclusion of every 10 patients is planned to address safety issues. This analysis focuses on the secondary endpoints and SAEs only, especially the rate of death during the hospital stay. During the interim analysis, the recruitment for the EARLYDRAIN study is not stopped.

Randomization:

Randomization is performed via a dedicated internet site accessible for all local investigators of the participating trial centers (www.randomizer.at). Application of a lumbar drain is performed accordingly, while the patient is still under anesthesia for aneurysm treatment.

At each participating center, a local database of all patients treated with aneurysmal SAH is to be established. In this database, reasons for patient exclusion should be documented (e.g. missing consent, aneurysm treatment not possible in the first 48 hours after aneurysmal SAH).

Study duration and other time points

Planned start of the study is Spring 2010. Depending on center participation and patient recruitment, inclusion of 300 patients is expected to be finished in summer 2011. As the main endpoint of the study is the MRS after 6 months, study completion is planned by the end of 2011. Data gathering and analysis is planned to be finished Spring 2012. Preparation and submission of a manuscript describing the results to a leading international Journal is planned in summer 2012.

Intellectual properties

The principal investigators retain the rights for first and last authorship of the manuscript containing the main results. The local investigators of the participating centers are granted access to the anonymized whole data set as well as co-authorship on the manuscript with the main results. The rank of co-authorship is determined by decreasing inclusion frequency. A separate trial contract is performed between a participating center and the principal investigators.

Data monitoring and surveillance site

The study is monitored by the Centrum für Schlaganfallforschung of the Charite, Humboldt University Berlin:

CSB Sekretariat

Charité - Universitätsmedizin Berlin

Campus Mitte

Charitéplatz 1

10117 Berlin

Fon +49 30 450 560 606

Fax +49 30 450 560 952

csb@charite.de

A dedicated study nurse visits the participating centers according to their recruiting frequency. During this visit, the clinical files of a recruited patient are reviewed on their consistancy with the EARLYDRAIN data sheet. The study center performs the telephone interviews for outcome assessment.

References:

1. Keyrouz SG, Diringer MN. Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. Crit Care 2007;11(4):220.

2. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, Kasuya H, Wellman G, Keller E, Zauner A, Dorsch N, Clark J, Ono S, Kiris T, Leroux P, Zhang JH. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurol. Res 2009;31(2):151-158.

3. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB, Dorsey FC, Ingram CR, Mellits DE, Bertsch LA, Boisvert DP, Hundley MB, Johnson RK, Strom JA, Transou CR. Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N. Engl. J. Med 1983;308(11):619-624.

4. Otten ML, Mocco J, Connolly ES, Solomon RA. A review of medical treatments of cerebral vasospasm. Neurol. Res 2008 Jun;30(5):444-449.

5. Komotar RJ, Hahn DK, Kim GH, Starke RM, Garrett MC, Merkow MB, Otten ML,

Sciacca RR, Connolly ES. Efficacy of lamina terminalis fenestration in reducing shunt-dependent hydrocephalus following aneurysmal subarachnoid hemorrhage: a systematic review. Clinical article. J. Neurosurg 2009;111(1):147-154.

6. Kasuya H, Shimizu T, Kagawa M. The effect of continuous drainage of cerebrospinal fluid in patients with subarachnoid hemorrhage: a retrospective analysis of 108 patients. Neurosurgery 1991;28(1):56-59.

7. Widenka DC, Wolf S, Schürer L, Plev DV, Lumenta CB. Factors leading to hydrocephalus after aneurysmal subarachnoid hemorrhage. Neurol. Neurochir. Pol 2000;34(6 Suppl):56-60.

8. Klimo P, Kestle JRW, MacDonald JD, Schmidt RH. Marked reduction of cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage. J. Neurosurg 2004;100(2):215-224.

9. Kwon OY, Kim Y, Kim YJ, Cho CS, Lee SK, Cho MK. The Utility and Benefits of External Lumbar CSF Drainage after Endovascular Coiling on Aneurysmal Subarachnoid Hemorrhage. J Korean Neurosurg Soc 2008;43(6):281-287.

10. Tizi K, Güresir E, Beck J, Raabe A, Seifert V, Vatter H. The effect of lumbar drainage on cerebral vasospasm and infarction after subarachnoid haemorrhage (abstract). 60th annual meeting of the German Society of Neurosurgery (DGNC) 2009;

11. Tuettenberg J, Czabanka M, Horn P, Woitzik J, Barth M, Thomé C, Vajkoczy P, Schmiedek P, Muench E. Clinical evaluation of the safety and efficacy of lumbar cerebrospinal fluid drainage for the treatment of refractory increased intracranial pressure. J. Neurosurg 2009;110(6):1200-1208.

12. Rankin J. Cerebrovascular accidents in patients over the age of 60: prognosis. Scott Med J 1957;(2):200-215.

13. Lindley RI, Waddell F, Livingstone M, Sandercock P, Dennis MS, Slattery J, Smith B, Warlow C. Can Simple Questions Assess Outcome after Stroke? Cerebrovasc Dis

1994;4(4):314-324.

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

15. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 1980;6(1):1-9.

16. Scheithauer S, Bürgel U, Ryang Y, Haase G, Schiefer J, Koch S, Häfner H, Lemmen S. Prospective surveillance of drain associated meningitis/ventriculitis in a neurosurgery and neurological intensive care unit. Journal of Neurology, Neurosurgery & Psychiatry 2009 Dec;80(12):1381-1385.

17. Molyneux AJ, Kerr RSC, Yu L, Clarke M, Sneade M, Yarnold JA, Sandercock P. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366(9488):809-817.

18. Kreiter KT, Mayer SA, Howard G, Knappertz V, Ilodigwe D, Sloan MA, Macdonald RL. Sample size estimates for clinical trials of vasospasm in subarachnoid hemorrhage. Stroke 2009 Jul;40(7):2362-2367.