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Original Research Article

A Randomized Clinical Study to Assess the Effectiveness of Lumbar Cerebrospinal Fluid Drainage (LCSFD) for Prevention of Cerebral Vasospasm and its Sequelae

Gaurav Batra[1], Sachin Kumar Singh[2], Girish K.M[3]

[1]Post MCh Senior Resident, Department of Neurosurgery, Govt. T.D. Medical College & Hospital, Alappuzha, Kerala, India.

[2]Post MCh Senior Resident, Department of Neurosurgery, Govt. T.D. Medical College & Hospital, Alappuzha, Kerala, India.

[3]Professor and HOD, Department of Neurosurgery, Govt. T.D. Medical College & Hospital, Alappuzha, Kerala, India.

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Corresponding author: Dr. Sachin Kumar Singh

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Abstract

Aim: The aim of the present study was to evaluate the effectiveness of lumbar cerebrospinal fluid drainage (LCSFD) for prevention of cerebral vasospasm and its sequelae.

Methods: This was a prospective, randomized control trial conducted at Department of Neurosurgery for 12 months . Patients of aneurysmal SAH (Hunt and Hess Grade II–IV) and 50 patients met the inclusion criteria and were randomly allocated to one of the two groups – thirty patients in Group I and thirty patients in Group II.

Results: There were 25 patients in each group. Both groups were matched with respect to age, sex, GCS on admission, and SAH grade at admission. Clinical evidence of vasospasm and rising TCD velocities suggestive of vasospasm developed in 28% (7/25) patients in LCSFD group compared to 64% (16/25) patients in non-LCSFD group and this difference was found statistically significant (P = 0.01). Although more number of patients in Group II developed hemiparesis was more due to vasospasm compared to Group I, this difference was not found to be statistically significant. The patient outcome as quantified by GOS at the time of discharge was better in LCSFD group (median GOS = 4) as compared to non-LCSFD group (median GOS = 3) and this difference was found to be statistically significant (P = 0.01). Median GOS at 1- and 3-month follow-up was 5 in Group I compared to 4 in Group II and this difference was statistically significant (P = 0.04).

Conclusion: This study has demonstrated the efficacy of LCSFD to significantly reduce clinical vasospasm and vasospasm-related cerebral infarction in patients with aneurysmal SAH, thereby contributing to a better outcome. Lumbar CSF drainage is believed to decrease cerebral vasospasm by promoting circulation of CSF and clearance of blood from the subarachnoid spaces.

Keywords: Aneurysm, Lumbar Cerebrospinal Fluid Drainage, Subarachnoid Hemorrhage, Vasospasm.

Introduction

Subarachnoid hemorrhage from the rupture of an intracranial aneurysm is a type of stroke leading to death or permanent disability in most affected patients. [1,2] For decades, cerebral vasospasm triggered by the amount of blood in the basal cisterns was regarded as causal for delayed cerebral ischemia. [3] Approximately70%of patients with subarachnoid hemorrhage develop vasospasm; up to 40% experience secondary infarction, part of these without vasospasm. Treatment of vasospasm in the large cerebral arteries did not improve mortality or functional outcome. [4,5] Prophylaxis with the calcium channel blocker nimodipine does not affect the cerebral vasculature but lessens poor outcome by one-third. [6]

It is common standard to occlude the culprit aneurysm by surgical clipping or endovascular coiling within 24 to 48 hours after hemorrhage, with coiling being preferred if both methods are equally feasible. [7] Efforts to remove the blood in the basal cisterns as the causative agent for vasospasm by surgery, cisternal, or external ventricular drainage showed mixed results. [8-10] In retrospective studies, prophylactic lumbar drainage of cerebrospinal fluid was associated with favorable outcome. [11,12] A plausible mechanism of action is increased removal of blood and its

degradation products using gravity. However, the prospective Lumbar Drainage in Subarachnoid Haemorrhage (LUMAS) trial randomizing 210 patients was unable to confirm a benefit of lumbar drains. [13] In hindsight, it recruited less severely affected patients with lower risk of adverse outcomes and may thus have been underpowered to detect a significant effect.

Subsequently, external ventricular drainage (EVD) and CSF lumbar drainage are both considered helpful in reducing vasospasm; alongside the primary purpose of CSF diversion in management of acute hydrocephalus following a SAH. These both indirectly help to clear blood clots in basal cisterns and accelerate the renewal of CSF. Recent study has shown that blood and CSF acidosis are the most troubling complication in a SAH through a cascade of pathophysiology changes. By promoting CSF renewal, EVD or lumbar drainage can renormalize acid-neutral CSF. [14] This explains the rationale behind these practices. Although the risk of infection in both procedures is equal, CSF lumbar drainage has lower risk of intra-cerebral hemorrhage and faster blood clot clearance. [15] Moreover, Klimo et al [16] revealed a significant reduction of incidence of vasospasm after aSAH with CSF lumbar drainage group compared to EVD group.

The aim of the present study was to evaluate the effectiveness of lumbar cerebrospinal fluid drainage (LCSFD) for prevention of cerebral vasospasm and its sequelae.

Materials and Methods

This was a prospective, randomized control trial conducted at department of neurosurgery, Govt. T.D. Medical College & Hospital, Alappuzha, Kerala, India for 12 months . Patients of aneurysmal SAH (Hunt and Hess Grade II–IV) and 50 patients met the inclusion criteria and were randomly allocated to one of the two groups – thirty patients in Group I and thirty patients in Group II.

- Group I: Underwent placement of Lumbar CSF drain
- Group II: Lumbar CSF drain was not placed.

Inclusion Criteria

1. All patients with aneurysmal SAH Hunt and Hess
2. Grade II–IV with ictus within 10 days before admission.

Exclusion Criteria

1. Evidence of raised intracranial pressure in the perioperative period contradicting placement of lumbar intrathecal drains.
2. Nonoperated patients where the aneurysm is not secured.
3. 3. Intracranial mass lesions, e.g., hematoma, cerebral edema, brain shift, etc.
4. Meningitis contradicting placement of intrathecal drains
5. Patients with Hunt and Hess Grade I and V SAH
6. Patients undergoing coiling.

Clinical management

All patients were assigned a Hunt and Hess grade at the time of admission according to neurological parameters. The patients were also assigned a Fisher's grade based upon thickness of subarachnoid clot on computed tomography (CT) scan of head. At admission, all patients were resuscitated and stabilized. The patients with poor neurological status with poor respiratory effort were intubated. With the exception of CSF drainage, all patients received treatment according to a consistent protocol. This included early surgical occlusion of the ruptured aneurysm (within 3 days following admission). The LCSFD was placed at the time of induction before craniotomy and was kept in place for next 72 h post procedure.

Patients in whom lumbar drain was placed were given antibiotics as per the protocol (Cefoperazone + sulbactam 1 gm 12 hourly, netilmicin 300 mg OD, Metrogyl 500 mg iv 8 hourly). Prophylactic 3H therapy was given depending on the clinical situation, administration of nimodipine, daily transcranial Doppler (TCD) ultrasonography examinations, rigorous monitoring, correction of electrolyte and blood gas abnormalities and management of hydrocephalus were carried out accordingly in both the groups.

Vasospasm was diagnosed using the criteria defined in the tirilazad trials:[17,18]

1. Deficits such as confusion, disorientation, drowsiness, or focal motor deficit during post hemorrhage days 4–14.
2. Negative findings on CT scans obtained to rule out other causes of neurological deterioration such as hemorrhage, cerebral edema, or hydrocephalus.
3. No other identifiable cause of neurological deterioration such as hyponatremia (Na <132 mEq/L), hypoxia, drug toxicity, infection, or seizures
4. Evidence of vasospasm on serial TCD examinations.

Cerebral infarction caused by vasospasm was diagnosed if either a delayed ischemic deficit became sustained beyond the risk period of cerebral vasospasm or if imaging studies revealed a region of cerebral infarction in a vascular territory consistent with the patient's vasospasm.

Lumbar cerebrospinal fluid drainage methods

In all patients randomized under the LCSFD group, closed system lumbar CSF drain was typically placed in the operating room at the time of surgery through L3– L4 intervertebral space after induction and was clamped. Before the dural opening, lumbar drain was opened up to release CSF and to facilitate brain relaxation. LCSFD was continued for next 72 h. The CSF bag was typically kept at the level of head to avoid over drainage of CSF.

Outcome Measures

There were four primary outcome measures in this study:

1. Clinically evident vasospasm
2. Vasospasm-related cerebral infarction
3. Condition of the patient at the time of discharge
4. Glasgow outcome score (GOS) score at 1- and 3-month follow-up.
5. Secondary outcome measures included duration of stay in Intensive Care Unit and overall hospital stay.

Results

Table 1: Demographic profile of the two groups

Parameters analyzed	Lumbar CSF drainage group	Non‑Lumbar CSF drainage group	*P*
Number of patients	25	25	-
Age in years (mean±SD) Range Sex (male:female)	46.4±10.4 30-70 10:15	45.5±11.3 18-75 12:13	0.78 0.82
GCS on admission (minimum-maximum) Mean	13.87±0.36 (12-15)	15.05±0.65 (12-15)	0.25
Median Comorbid illness (%) HTN	14 (12-15) 15 (60)	14 (12-15) 12 (48)	0.45
DM	1 (4)	1 (4)	
Bronchial asthma	0	1 (4)	
CAD	1 (4)	0	
Valvular heart diseaseSAH grade (%) II	0 9 (36)	1 (3.3) 13 (52)	 0.55
III	12 (48)	9 (36)	
IV Aneurysmal bleed (%)ACom	4 (16) 14 (56)	3 (12) 14 (56)	 0.75
DACA	1 (4)	3 (12)	
MCA	5 (20)	2 (8)	
PCom	0	1 (4)	
ICA	4 (16)	4 (16)	
AICA	1 (4)	1 (4)	

There were 25 patients in each group. Both groups were matched with respect to age, sex, GCS on admission, and SAH grade at admission.

Table 2: Summarizing the results in two groups

Parameters analyzed	Lumbar CSF drainage group (%)	Non‑Lumbar CSF drainage group (%)	*P*
Clinical effect of vasospasm	7/25	16 (64)	0.01
Focal neurological deficit Hemiparesis	5/25	9 (36)	0.17
Quadriparesis	0	1 (4)	1
Monoparesis	0	1 (4)	1
Paraparesis	0	1 (4)	1
TCD effect of vasospasm	8/25 (32)	16 (64)	0.01
Radiological effect of vasospasm (vasospasm-related cerebral infarction)	5/25 (20)	14/25 (56)	0.007
Perioperative complications Meningitis	4/25 (16)	2 (8)	0.42
Pneumonia	3/25 (12)	3 (12)	1
UTI	0	1 (3.3)	1
Septicemia	1/30 (3.3)	2/25 (8)	1
Dyselectrolytemia	2/30 (6.7)	2/25 (8)	1
Hypoxia	0	0	-
Development of extradural/ subdural	1/25 (4)	0	0.5

hemorrhage/ effusion requiring evacuation			
Development of hydrocephalus	2/25 (8)	2/25 (8)	1
Mortality	2/28 (8)	2/25 (8)	1

Clinical evidence of vasospasm and rising TCD velocities suggestive of vasospasm developed in 28% (7/25) patients in LCSFD group compared to 64% (16/25) patients in non-LCSFD group and this difference was found statistically significant (P = 0.01). Although more number of patients in Group II developed hemiparesis was more due to vasospasm compared to Group I, this difference was not found to be statistically significant.

Table 3: Summarizing the outcome between the two groups

Parameters analyzed	Lumbar CSF drainage group (%)	Non‑Lumbar CSF drainage group (%)	*P*
GCS at the time of discharge (range) Mean	13.87±0.27 (14-15)	14.46±1.43 (9-15)	0.11
Median GOS at the time of discharge Mean	15 (14-15) 3.85±1.02 (1-5)	15 (9-15) 3.32±0.80 (1-5)	0.01
Median	4 (1-5)	3 (1-5)	
Median duration of ICU stay in days (range)	7.5 (3-20)	8 (3-14)	0.91
Median duration of hospital stay in days (range)	12 (7-31)	12 (6-45)	0.74
GOS at 1 month follow-up Mean	4.6±1.07 (1-5)	3.90±0.93 (1-5)	0.04
Median GOS at 3 months follow-up Mean	5 (1-5) 4.4±(1-5)	4 (1-5) 3.86±0.93 (1-5)	0.04
Median	5 (1-5)	4 (1-5)	

The patient outcome as quantified by GOS at the time of discharge was better in LCSFD group (median GOS = 4) as compared to non-LCSFD group (median GOS = 3) and this difference was found to be statistically significant (P = 0.01). Median GOS at 1- and 3-month follow-up was 5 in Group I compared to 4 in Group II and this difference was statistically significant (P = 0.04).

Discussion

Many treatment modalities have emerged over the years to prevent cerebral vasospasm. Foremost among these modalities was the introduction of triple‑H (3H) therapy in the early 1980s. [19,20] Nimodipine, which was introduced for widespread clinical use in 1985, reduced the overall percentage of patients with severe vasospasm from 30% to 20%; however, it does not seem to decrease the incidence of vasospasm identified on angiography. [21-23]

There were 25 patients in each group. Both groups were matched with respect to age, sex, GCS on admission, and SAH grade at admission. Clinical evidence of vasospasm and rising TCD velocities suggestive of vasospasm developed in 28% (7/25) patients in LCSFD group compared to 64% (16/25) patients in non-LCSFD group and this difference was found statistically significant (P = 0.01). Although more number of patients in Group II developed hemiparesis was more due to vasospasm compared to Group I, this difference was not found to be statistically significant. The patient outcome as quantified by GOS at the time of discharge was better in LCSFD group (median GOS = 4) as compared to non-LCSFD group (median GOS = 3) and this difference was found to be statistically significant (P = 0.01). Median GOS at 1- and 3-month follow-up was 5 in Group I compared to 4 in Group II and this difference was statistically significant (P = 0.04). There are numerous clinical studies which revealed that early surgical removal of blood clots and irrigation of subarachnoid spaces may reduce the risk of cerebral vasospasm [24-26] however, the clinical results have not been satisfactory because it is very difficult to remove the clot completely in the acute stage after SAH and may even be hazardous. [27,28] It has also been well documented that the amount of subarachnoid clot is closely related to the incidence and severity of vasospasm. [26,27] In his original article published in 1980, Fisher had shown that the amount of blood within the basal cisterns on a CT scan correlated with the development of angiographic vasospasm. When the subarachnoid blood was not detected or <1 mm thick (Fisher Grade I, II), severe vasospasm was rare (1 of 18 cases). In Fisher Grade III, severe spasm followed almost invariably (23 of 24 cases). [29] This was confirmed by subsequent studies. [30,31] More recently, it was found that the relative risk for symptomatic vasospasm was 5.1 for patients with Fisher Grade III SAH (95% confidence interval, 2.0–13.1; P = 0.008). [32] Experimental studies in which a primate model was used showed that clot removal within 48 h of SAH prevented vasospasm.

Klimo et al [27] in a prospective nonrandomized trial involving 167 patients concluded that the LCSFD was superior to ventricular CSF drainage in the management of vasospasm. Symptomatic vasospasm occurred in 17% and 51% of patients with and without LCSFD, respectively, indicating that external clearance of spasmogenic substances

reduces vasospasm in patients with thick SAH. Shunting of CSF through a lumbar drain conferred a statistically significant advantage with respect to marked reduction in the risk of clinically evident vasospasm and its sequelae, shortening of hospital stay, and improvement in outcome. In comparison with ventricular CSF drainage, LCSFD is more safe without being a direct cause of brain parenchymal damages such as intracranial hemorrhage.

Conclusion

This study, which followed a prospective and randomized controlled design, has provided evidence of the effectiveness of LCSFD in dramatically decreasing clinical vasospasm and vasospasm-related cerebral infarction in individuals diagnosed with aneurysmal subarachnoid haemorrhage (SAH). As a result, this intervention has the potential to improve patient outcomes. The current understanding suggests that lumbar cerebrospinal fluid (CSF) drainage can potentially reduce cerebral vasospasm by facilitating the circulation of CSF and the removal of blood from the subarachnoid spaces. The LCSFD is potentially correlated with the occurrence of meningitis. Patients who undergo LCSFD require proper care and the administration of suitable antibiotics in order to prevent the occurrence of infection.

References

1. Nieuwkamp DJ, Setz LE, Algra A, Linn FHH, de Rooij NK, Rinkel GJE. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: ameta-analysis. Lancet Neurol. 2009;8(7):635-642.
2. Lovelock CE, Rinkel GJE, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: population-based study and systematic review. Neurology. 2010; 74(19): 1494-1501.
3. Macdonald RL. Origins of the concept of vasospasm. Stroke. 2016;47(1):e11-e15.
4. Macdonald RL, Higashida RT, Keller E, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011; 10(7):618-625.
5. Macdonald RL, Higashida RT, Keller E, et al. Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling. Stroke. 201 2;43(6):1463-1469.
6. Dorhout Mees SM, Rinkel GJE, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007; 2007(3):CD000277.
7. Molyneux A, Kerr R, Stratton I, et al; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 2002;360(9342):1267-1274.
8. Mao J, Zhu Q, Ma Y, Lan Q, Cheng Y, Liu G. Fenestration of lamina terminalis during anterior circulation aneurysm clipping on occurrence of shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage: meta-analysis. World Neurosurg. 2019;129: e1-e5.
9. Roelz R, Schaefer JH, Scheiwe C, et al. Impact of stereotactic ventriculocisternostomy on delayed cerebral infarction and outcome after subarachnoid hemorrhage. Stroke. 2020; 51(2): 431-439.
10. 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.
11. Grossen AA, Ernst GL, Bauer AM. Update on intrathecal management of cerebral vasospasm: a systematic review and meta-analysis. Neurosurg Focus. 2022;52(3):E10.
12. Hulou MM, Essibayi MA, Benet A, Lawton MT. Lumbar drainage after aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis.World Neurosurg. 2022;16 6:261-267.e9.
13. Al-Tamimi YZ, Bhargava D, Feltbower RG, et al. Lumbar drainage of cerebrospinal fluid after aneurysmal subarachnoid hemorrhage: a prospective, randomized, controlled trial (LUMAS). Stroke. 2012;43(3):677-682.
14. Demirci T, Aydin MD, Caglar O, Aydin N, Ozmen S, Nalci KA, Ahiskalioglu A, Kocak MN, Keles S. First definition of burned choroid plexus in acidic cerebrospinal fluid-filled brain ventricles during subarachnoid hemorrhage: Experimental study. Neuropathology. 2020 Jun;40(3):251-60.
15. Maeda Y, Shirao S, Yoneda H, Ishihara H, Shinoyama M, Oka F, Sadahiro H, Ueda K, Sano Y, Kudomi S, Hayashi Y. Comparison of lumbar drainage and external ventricular drainage for clearance of subarachnoid clots after Guglielmi detachable coil embolization for aneurysmal subarachnoid hemorrhage. Clinical Neurology and Neurosurgery. 2013 Jul 1;115(7):965-70.
16. Klimo P, Kestle JR, MacDonald JD, Schmidt RH. Marked reduction of cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage. Journal of neurosurgery. 2004 Feb 1;100(2):215-24.

17. Findlay JM, Kassell NF, Weir BK, Haley Jr EC, Kongable G, Germanson T, Truskowski L, Alves WM, Holness RO, Knuckey NW, Yonas H. A randomized trial of intraoperative, intracisternal tissue plasminogen activator for the prevention of vasospasm. Neurosurgery. 1995 Jul 1;37(1):168-78.
18. Kassell NF, Torner JC, Haley EC, Jane JA, Adams HP, Kongable GL. The international cooperative studyon the timing of aneurysm surgery: Part 1: Overall management results. Journal of neurosurgery. 1990 Jul 1;73(1):18-36.
19. Awad IA, Carter LP, Spetzler RF, Medina M, Williams Jr FC. Clinical vasospasm after subarachnoid hemorrhage: response to hypervolemic hemodilution and arterial hypertension. Stroke. 1987 Mar;18(2):365-72.
20. Origitano TC, Wascher TM, Reichman HO, Anderson DE. Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. Neurosurgery. 1990 Nov 1;27(5):729-40.
21. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB. Cerebral arterial spasm–a controlled trial of nimodipine in patients with subarachnoid hemorrhage. New England Journal of Medicine. 1983 Mar 17;308(11):619-24.
22. Barker FG, Ogilvy CS. Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. Journal of neurosurgery. 1996 Mar 1;84(3):405-14.
23. Feigin VL, Rinkel GJ, Algra A, Vermeulen M, Van Gijn J. Calcium antagonists in patients with aneurysmal subarachnoid hemorrhage: a systematic review. Neurology. 1998 Apr 1;50 (4):876-83.
24. Inagawa T, Kamiya K, Matsuda Y. Effect of continuous cisternal drainage on cerebral vasospasm. Acta neurochirurgica. 1991 Mar; 112:28-36.
25. Mizoi K, Yoshimoto T, Takahashi A, Fujiwara S, Koshu K, Sugawara T. Prospective study on the prevention of cerebral vasospasm by intrathecal fibrinolytic therapy with tissue-type plasminogen activator. Journal of neurosurgery. 1993 Mar 1;78(3):430-7.
26. Kawamoto S, Tsutsumi K, Yoshikawa G, Shinozaki MH, Yako K, Nagata K, Ueki K. Effectiveness of the head-shaking method combined with cisternal irrigation with urokinase in preventing cerebral vasospasm after subarachnoid hemorrhage. Journal of neurosurgery. 2004 Feb 1;100(2):236-43.
27. Klimo P, Kestle JR, MacDonald JD, Schmidt RH. Marked reduction of cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage. Journal of neurosurgery. 2004 Feb 1;100(2):215-24.
28. Sasaki T, Kodama N, Kawakami M, Sato M, Asari J, Sakurai Y, Watanabe K, Onuma T, Matsuda T. Urokinase cisternal irrigation therapy for prevention of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage: a study of urokinase concentration and the fibrinolytic system. Stroke. 2000 Jun;31(6):1256-62.
29. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980 Jan 1;6(1):1-9.
30. Rabb CH, Tang G, Chin LS, Giannotta SL. A statistical analysis of factors related to symptomatic cerebral vasospasm. Acta neurochirurgica. 1994 Mar; 127:27-31.
31. Inagawa T. Cerebral vasospasm in elderly patients treated by early operation for ruptured intracranial aneurysms. Acta neurochirurgica. 1992 Sep; 115:79-85.
32. Lasner TM, Weil RJ, Riina HA, King JT, Zager EL, Raps EC, Flamm ES. Cigarette smoking—induced increase in the risk of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. Journal of neurosurgery. 1997 Sep 1;87(3):381-4.