

The Effect of Choroidal Artery Vasospasm on Choroid Plexus Injury in Subarachnoid Hemorrhage: Experimental Study

Subaraknoid Kanamada Koroidal Arter Vazospazmının Koroid Pleksus Hasarı Üzerine Etkisi: Deneysel Çalışma

Adem YILMAZ¹, Mehmet Dumlu AYDIN², Ayhan KANAT³, Ahmet Murat MUSLUMAN¹, Sare ALTAS⁴, Yunus AYDIN¹, Muhammet CALIK⁴, Nesrin GURSAN⁴

¹Sisli Etfal Education and Research Hospital, Department of Neurosurgery, Istanbul, Turkey

²Ataturk University, Faculty of Medicine, Department of Neurosurgery, Erzurum, Turkey

³Rize University, Faculty of Medicine, Department of Neurosurgery, Rize, Turkey

⁴Ataturk University, Faculty of Medicine, Department of Pathology, Erzurum, Turkey

Presented in: Annual Scientific Congress of Turkish Neurosurgical Society, Antalya, Turkey, 14-18 May 2010.

Correspondence address: Mehmet Dumlu AYDIN / E-mail: nmda11@hotmail.com

ABSTRACT

AIM: We examined whether vasospasm of choroidal arteries (ChAs) may be resulted in ischemic injury in choroid plexus (CP) after subarachnoid hemorrhage (SAH).

MATERIAL and METHODS: This study has been conducted on 30 rabbits. Eight, fourteen and eight of them were used as control, SAH and SHAM groups, respectively. The volumes of choroidal arteries were examined and measured by using the micrometric microscope barr. Ischemic morphological changes of the choroid plexus cells and villus were examined as follows: cellular shrinkage (1 point), cytoplasmic condensation (2 points), angulation (3 points) and villus desquamation (4 points) were considered as 1st, 2nd, 3rd, 4th degree downward choroid plexus degeneration criteria. Degeneration scores of 1 to 4 criteria were calculated by summing the exacerbated ones with the existing one.

RESULTS: Choroidal artery diameter&volume, and CP degeneration scores in three groups were evaluated: The mean volumes were $1.080 \pm 0.650 \text{ mm}^3$, $0.907 \pm 0.330 \text{ mm}^3$, $0.480 \pm 0.175 \text{ mm}^3$ and the degeneration scores of choroidal plexuses were scored as 0 and 1- 1, and 4- 3 and 10 in the control, SHAM and SAH groups respectively. A significant correlation between the degree of vasospasm and CP degeneration was found.

CONCLUSION: Vasospasm of choroidal arteries may be at a serious degree in cases with SAH incurs damages on choroid plexuses, and affects structures which play important roles in immune, endocrine, detoxifying, thermoregulatory, and secretory functions of the brain resulting in worsened prognosis.

KEYWORDS: Choroidal artery, Vasospasm, Choroid plexus injury, Subarachnoid hemorrhage, Rabbit

ÖZ

AMAÇ: Bu çalışmada, subaraknoid kanamada (SAK) koroid arter vazospazmının koroid pleksusta (KP) iskemik hasar yapıp yapmadığını inceledik.

YÖNTEM ve GEREÇLER: Bu çalışma 30 tavşan üzerinde yapıldı. Sekizi kontrol grubu, 14'ü SAK grubu, 8 tavşan da SHAM grubu olarak kullanıldı. Koroidal arterlerin tam koroid pleksusa girdiği noktadaki kesitlerinin çapı ve volümü mikrometrik mikroskop kullanılarak ölçüldü. Koroid pleksus hücre ve villuslarının iskemik morfolojik değişiklikleri hafiften ağıra doğru şu şekilde tanımlandı: hücresel küçülme (1 puan), sitoplazmik yoğunlaşma (2 puan), angulasyon (3 puan) ve villus yıkımı (4 puan). Mevcut histopatolojik bulguların 1 ile 4 arasındaki dejenerasyon kriterlerinin toplamı dejenerasyon skoru olarak tanımlandı. Sonuçlar istatistiksel olarak değerlendirildi.

BULGULAR: Üç grubun koroidal arter çapı ve volümü ile dejenerasyon skoru değerleri şu şekilde bulundu. Kontrol grubunda ortalama koroidal arter çapı $120 \pm 30 \mu\text{m}$, volümü $1,080 \pm 0,650 \text{ mm}^3$ ve dejenerasyon skoru 0 ve 1 arasında idi. SHAM grubunda ortalama koroidal arter çapı $110 \pm 20 \mu\text{m}$, volümü $0,907 \pm 0,330 \text{ mm}^3$ ve dejenerasyon skoru 1 ve 4 arasında idi. SAK grubunda ortalama koroidal arter çapı $80 \pm 15 \mu\text{m}$, volümü $0,480 \pm 0,175 \text{ mm}^3$ ve dejenerasyon skoru 3 ve 0 arasında idi. Sonuçta vazospazm derecesi ile KP dejenerasyonu arasında anlamlı ilişki bulundu.

SONUÇ: SAK olgularında koroidal arterlerin vazospazmı değişik derecelerde koroid pleksus hasarı oluşturabilir. Beynin immün, endokrin, detoksifikasyon, termoregulasyon ve sekretuar fonksiyonlarında önemli rolü olan koroid pleksusların hasar görmesi SAK'daki kötü prognozun önemli bir sebebi olabilir.

ANAHTAR SÖZCÜKLER: Koroidal arter, Vazospazm, Koroid pleksus hasarı, Subaraknoid kanama, Tavşan

INTRODUCTION

Cerebral vasospasm is one of the most challenging complications following subarachnoid hemorrhage (SAH). Although cerebral vasospasm after SAH has been the subject of substantial research interest, the underlying pathogenic mechanisms remain obscure (4,5,22,23). Because of delayed narrowing of large-capacity arteries of the brain, cerebral vasospasm is one of the leading causes of morbidity and death following SAH (2). One of these arteries are the choroidal arteries (ChAs).

Choroid plexuses (CP) are brain structures located in the brain ventricles. They are comprised of highly vascularised villi and ciliated modified ependyma. The CP is highly vulnerable to damage in head injuries, infections and ischemic conditions (10,11). Although it is generally accepted at the present time that the choroid plexuses (CP) are the main source of the cerebrospinal fluid, nothing is to be found in the literature concerning the vasospasm of choroid plexus artery and injury of the plexus. The experiments about this subject may have shown the difficulties which beset attempts to draw conclusions. The situation and relationships of the plexus must always make the performance of such experimental studies difficult and the interpretation of the results uncertain and inconclusive (20,26). We hypothesized that the choroidal artery vasospasm after SAH may be resulted in plexus injury. This could be lead to atrophy of choroid plexus and diminished cerebrospinal fluid (CSF) production. The diminished CSF production may be one of reasons of cerebral hyperthermia. Therefore, we examined the choroid plexus injury after choroidal artery vasospasm in experimental subarachnoid hemorrhage

MATERIAL and METHODS

This study was performed on 30 anesthetized adult male New Zealand rabbits. The animal protocols were approved by the Ethics Committee of Erzurum Atatürk University, Medical Faculty. The care of the animals and the experiments themselves were conducted according to the guidelines set forth by the same ethics committee. A balanced, injectable anesthetics were used in order to reduce pain and mortality. After anesthesia was induced with isoflurane given by a face mask, 0.2 mL/kg of the anesthetic combination (Ketamine HCL, 150 mg/1.5 mL; Xylazine HCL, 30 mg/1.5 mL; and distilled water, 1 mL) was subcutaneously injected before surgery. During the procedure, a dose of 0.1 mL/kg of the anesthetic combination was used when required.

Animals selection: Autologous blood (1 mL) was taken from the auricular artery and injected using a 22-Gauge needle into the cisterna magna of animals in the SAH group over the course of 1 minute for fourteen of thirty rabbits (n=14). Eight rabbits were selected for control group (n=8). One mL of physiologic serum was injected into the cisterna magna for eight of them as SHAM group (n=8). The animals were followed for 20 days without any medical treatment and then sacrificed. Whole bodies of all animals were kept

in 10% formalin solutions for 7 days after required cleaning procedures for retrograde histologic examination.

Histopathological Procedures: Morphological examinations of the brains showed that all ChAs the cisternal segment, extending from its origin to the choroidal fissure, and the plexal segment extending from the choroidal fissure to the area where it enters into the choroidal plexus on the temporal horn.

The choroid plexuses and ChAs were obtained from coronary sections of brains at the levels of temporal horns of lateral ventricles and stained with hematoxylin and eosin (H&E). Luminal diameters of anterior choroidal arteries branches just entering in choroid plexus were examined and measured by using the micrometric microscope barr.

Endothelial swellings, luminal narrowing and inner elastic membrane convolutions were accepted as ChAs vasospasm criteria. All ChAs were accepted as a cylinder because of their morphological characteristics, and simple geometric formulas were used to estimate their volumes. As a measure of the degree of vasospasm, ChA volume values were preferred to determining the degree of vasospasm, because volume estimation method can be readily performed, is intuitively simple, is more reliable, and is free from assumptions about vessel diameter in various segments and unaffected overprotection and truncation. Choroidal arteries sectioned twenty consecutive sections by 5 micron distances at the levels of just entering the choroid plexuses in all animals. Then 20 histopathological section were taken by microtome of 5 µm distances of each a, b, c, ... s, t. The lumen diameters of each 20 histologic sections levels were measured and shown as $2r_a, 2r_b, 2r_c, \dots, 2r_t$. The mean radius value of ChAs were calculated as $r = (r_a + r_b + r_c + \dots + r_t) / 20$. The heights of the ChA sections of 5 µm imagined as $h = h_a + h_b + h_c + \dots + h_t = 5h$ were accepted as the total height ($\Sigma h = h$) of the cylinder-shaped ChA samples. The mean volume values of all bilateral ChA were calculated using the following formula: $V = \pi r^2 h$. For example, mean diameter of chosen segmental model of ChAs were estimated as 120 µm and their heights was $5 \times 20 = 100 \mu\text{m}$. Estimated volume; $V = \pi r^2 h = \pi (60)^2 100 \mu\text{m}^3 = 3 \times 3600 \times 100 \mu\text{m}^3 = 1.080.000 \mu\text{m}^3 = 1.08 \text{mm}^3$.

Ischemic morphological changes of the choroidal cells and villus degeneration were examined as follows: cellular shrinkage (1), cytoplasmic condensation (2), angulation (3) and villus desquamation (4) were considered as 1st, 2nd, 3rd, 4th degree downward choroid plexus degenerations criteria. Degeneration scores of subjects expressed the degeneration of 1 to 4 criteria was calculated with summing the exacerbated ones with the existing one.

The differences between the ChAs volumes and degeneration scores of choroid plexus were compared statistically. For the statistical analysis, SPSS ver. 15.0 was used. The mean \pm standard deviation of the variables is reported. Since the data showed a normal distribution inter-group differences were assessed using a one-way ANOVA. The presence of

homogeneous variance necessitated the use of the Tukey test for comparisons between two groups. A $P < 0.05$ was accepted as statistically significant.

RESULTS

Two of the animals ($n=2$) died within the first week and the remaining ($n=28$) followed in 20 days without any medical treatment and then sacrificed. Clinically, meningeal irritation signs, consciousness, convulsive attacks, fever, apnea, cardiac arrhythmia, and breath disturbances were observed frequently in premortal periods of the dead animals and the five living animals. Frontal sections of brains shows white matter expansions and compressed lateral ventricles. In some cases blood clots were observed in lateral ventricles. Brain temperatures were measured high velocities in these cases because of choroid body injury and decreased CSF. Brain edema, stiffness, leptomeningeal thickness, brain swelling and increased brain weight were seen in all animals that developed subarachnoid hemorrhages (Figure 1). The mean length of the examined ChA was 0.35 ± 0.10 mm.

ChAs convolutions were more prominent in the animals with induced SAH than in the SHAM and control groups. In order to estimate ChAs volume, squared-lined glass plates

were used while photographs were taken under microscope during the histopathological examinations of the ChAs. The relationship between choroidal artery diameter and volume and CP degeneration scores were evaluated, according to the following criteria: In the control group ($n=8$), the mean diameter value of chosen segmental model of ChAs were estimated as $120 \pm 30 \mu\text{m}$ and their mean volume was $1,080 \pm 0,650 \text{mm}^3$ while the degeneration scores of choroidal plexuses were scored as 0 and 1 (Figure 2). In the SHAM group ($n=8$) mean diameter of these arteries was $110 \pm 20 \mu\text{m}$, and their mean volume was $0.907 \pm 0.330 \text{mm}^3$ and degeneration scores of choroid plexus ranging between 1 and 4. In the SAH induction group ($n=14$) mean diameter of choroidal arteries as $80 \pm 15 \mu\text{m}$, and their volume was $0.480 \pm 0.175 \text{mm}^3$ and degeneration scores of choroid plexus ranging between 3 and 10 (Figure 3) (Table I).

No difference between the volume of the choroidal artery and degeneration score of choroid plexus was observed in

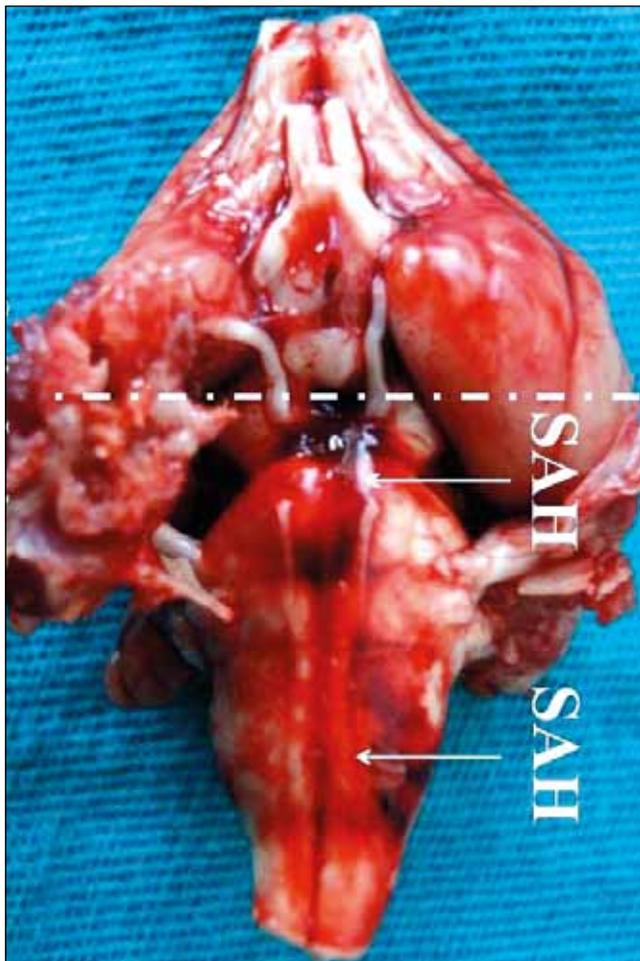


Figure 1: Macrobrain image with subarachnoid hemorrhage.

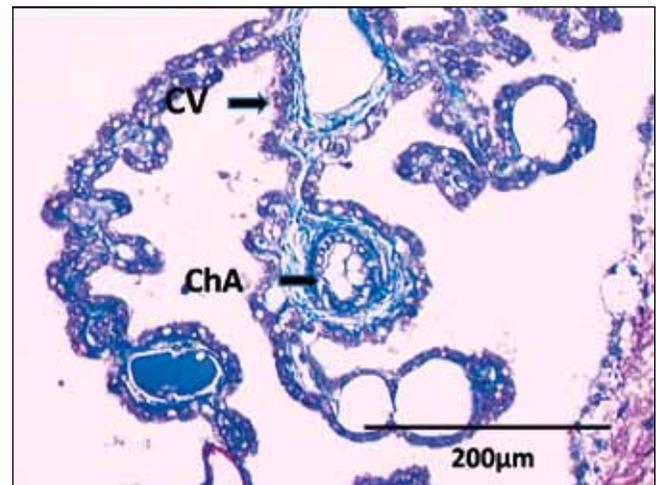


Figure 2: Choroidal plexus view in normal rabbit (ChA- Choroidal artery; CV-Choroid villi LM,H&E, x40).

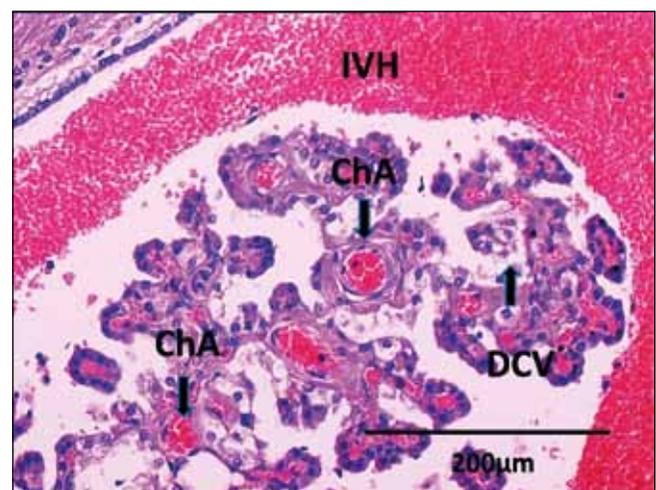


Figure 3: Choroid plexus and spastic choroidal artery view in rabbit with SAH (ChA- Choroid artery; DCV- Desquamated choroid villi; IVH- Intraventricular hemorrhage; LM,H&E, x40).

Table I: Correlation between the Degree of ChA Vasospasm, and Degeneration Scores

Group	Mean diameter of choroidal artery (µm)	Mean volume of choroidal artery (mm ³)	Degeneration score of choroid plexus
Control Group (n=8)	120±30µm	1.080±0.650mm ³ ^a	0—1 ^b
SHAM Group (n=8)	110±20µm	0.907±0.330mm ³ ^a	1—4 ^b
SAH Group (n=14)	80±15µm	0.480±0.175mm ³ ^b	3—10 ^a

There was a difference noted between the groups with different letters, while the groups represented by the same letter showed no significant differences.

the controls and the SHAM rabbits ($p>0.05$). However, the SAH group showed a difference ($p<0.05$). A significant correlation between the degree of vasospasm and degeneration criteria was found. We found that, a inverse relationship was observed between the volume of ChAs and degeneration scores of choroid plexus ($P<0.05$).

DISCUSSION

In the present experimental study, the effects of ChAs vasospasm on choroid plexus degeneration and apoptosis following SAH were firstly investigated.

CP are brain structures located in the lateral, third and fourth ventricles and form one of the interfaces between the blood and the central nervous system (CNS). They are comprised of highly vascularised villi covered by a ciliated modified ependyma. CP constitute up to 60% of the ventricular volume in the young but the volumes descend to a low percentage at the elderly (10). Choroid plexuses also participate in neurohumoral brain modulation and neuroimmune interactions, thereby contributing greatly in maintaining brain homeostasis (20,26). The plexus is supplied by anterior and posterior choroidal arteries. In general, the anterior choroidal artery supplies the more posterior part of the plexus while the posterior choroidal arteries supply the more anterior part. These also supply the optic tract, uncus, lateral part of geniculate body, posterior two-thirds of the posterior limbs of internal capsule, optic radiation and choroid plexus on the lateral ventricle. The classical features of ChAs occlusion are contralateral hemiplegia, hemianesthesia and hemianopsia. Also, these arteries' occlusion causes ischemic injury and apoptosis of choroid plexus (13,25,27).

Vasospasm is a pathophysiologic entity, characterized by narrowing of vascular lumen in varying degrees which might develop after SAH, and associated with higher rates of mortality and morbidity. It was defined as a combination of neurogenic response of adrenergic nervous system, and myogenic response of the arterial wall together with pharmacological reaction of the vessel wall against substances released from the circulating blood (8,24). The exact pathophysiology of vasospasm is very complex and poorly understood. Excessive production of free radicals and subsequent lipid peroxidation has been suggested causally related to cerebral vasospasm after SAH (6,9,14,15).

Clinical manifestations developing after vasospasm vary according to the degree, severity, location, and extent of

the vascular spasm. It mostly develops in the bleeding site, and surrounding vessels. Development of vasospasm usually occurs between 4th and 14th days of the vasospasm (19,27). In the early phase of vasospasm, acute ischemic changes were encountered in 30 % of the cases (17). The patients might be asymptomatic or manifest evidence of diffuse cerebral necrosis secondary to ischemic changes. As for approximate outcomes of studies performed in various centers mean incidence of death, and permanent disability have been indicated to be 7 percent (7,16). Although cerebral vasospasm after SAH has been the subject of substantial research interest, the underlying pathogenic mechanisms remain obscure (1,4,18,22). Therefore, different in vivo animal models have been developed in order to assess cerebral vasospasm and pharmacologically vasoactive effects. In the present study 2 out of 14 rabbits (14.2%) who developed SAH died during the experiment.

According to the literature, injection of fresh blood into the cisterna magna is one of the most commonly used methods to establish SAH in rabbits and has been found successful in obtaining a vasospasm (3,15). Experimental brain ischemia in rats caused a massive reduction in choroid plexus blood flow and marked disruption of the blood-CSF barrier, which may enhance the movement of compounds from blood to areas close to the ventricular system and participate in delayed neuronal death (12,26). Infarction of the CP probably has effects on CSF regulation with or without clinical manifestations (20,21). In the present study we examined choroidal arteries from rabbits with experimental SAH using cisternal blood injection model. In our study, we did not specifically examine a particular choroidal artery. Instead of the main choroidal artery, luminal diameters and volumes of choroidal arteries branches in choroid plexus have two layer muscle were measured. Among groups, volume of arteries in the SAH group were statistical significantly lower when compared with those of the control, and SHAM groups. Adverse effects of choroidal vasospasm on choroid plexus were evaluated according to the following degeneration criteria: (1) shrinkage of choroidal cells, (2) cytoplasmic condensation (3), angulation, and (4) villus desquamation. As a result, it was found that the choroidal artery diameter of SAH group was statistical significantly lower than SHAM and control groups. When the vasospasm got more serious, we saw that the degeneration scores was significantly increased ($p<0.05$).

Rational of the Present Study: It was the main object of this investigation to ascertain whether the arrangement of the vessels in the choroid plexus suggested any point at which nervous control of the plexus might be effected after SAH. CP functions are important and numerous. Choroid tissues belong to the hemato-encephalic barrier. Metabolic activity of CPs is estimated to be half that of the kidneys. The plexuses secrete about 90% of CSF; the remaining 10 % comes from brain interstitial fluid drainage. Brain is immersed in CSF, which confers mechanical protection and diminishes apparent weight according to Archimede's principle, as well as an unspecific sink for waste products from the CNS. CSF should not be considered as an inert and static fluid. It is renewed several times a day and is a medium for transportation of many molecules. It is used for elimination of by-products of cerebral catabolism and toxic compounds. CSF is similar to brain interstitial fluid. It is almost completely secreted by choroid plexus. These secretions are critical for maintaining water balance and therefore the brain volume. For that reason, normal function of CP is important. And in present study, it was first time reported that the vasospasm of CP artery might be effected the function of CP in SAH patients. It appears likely that the anterior and posterior choroidal artery or its choroidal branch after SAH was affected, so that the blood flow distal to that point is restricted. The least anatomically variable and clinically most important part of the anterior choroidal artery is the distal part, after the choroidal branch is given off, which supplies the lateral geniculate body. There is unlikely to be an arrangement whereby the blood supply to the geniculate body is determined by the requirements of the choroid plexus. Injury of plexus might be impaired the blood supply to geniculate body . Secondly, the choroidal branch divides immediately before entering the plexus into five or six branches, each almost as large as the parent stem. This reduces the length of the anterior and posterior choroidal artery where its circulation may be disturbed by a vasospasm after SAH. In our opinion the anatomical evidence of plexus injury after SAH shows that CSF production by plexus is affected.

CONCLUSION

Pathologic processes involving in vasospasm in SAH, also significantly affect choroidal arteries, resulting in ischemic injury and apoptosis of choroid plexus and decreased CSF secretion. Because cerebrospinal fluid cold the brain, decreased CSF secretion may cause increased brain temperature and hyperthermic brain injury in SAH. We conceive that impairment of these structures which with their secretion CSF, have important roles in cerebral nutrition, detoxification, cooling, enhancement of cerebral immunity with its immunoglobulin production, maintenance of endocrine secretory, and repository function, and regulation of blood-CSF pH, convey crucial significance in worsened prognosis in SAH.

ABBREVIATIONS

SAH: Subarachnoid hemorrhage

ChA: Choroidal artery

CP: Choroid plexus

CSF: Cerebrospinal fluid

CNS: Central nervous system

REFERENCES

1. Allen GS, Ahn HS, Presozi 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* 308: 619-624,1983
2. Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE Jr, Harbaugh RE, Patel AB, Rosenwasser RH: American Heart Association. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 40:994-1025, 2009
3. Belen D, Besalti O, Yigitkanli K, Kösemehmetoglu K, Simsek S, Bolay H: Leflunomide prevents vasospasm secondary to subarachnoid haemorrhage. *Acta Neurochir(Wien)* 149: 1041-1047, 2007
4. Buchanan KM, Elias LJ, Goplen GB: Differing perspectives on outcome after subarachnoid hemorrhage: The patient, the relative, the neurosurgeon. *Neurosurgery* 46: 831-838,2000
5. Carter BS, Buckley D, Ferraro R, Rordorf G, Ogilvy CS: Factors associated with reintegration to normal living after subarachnoid hemorrhage. *Neurosurgery* 46: 1326-1333, 2000
6. Cavallini L, Alexandre A: Oral N-acetylcysteine increases the production of anti-HIV chemokines in peripheral blood mononuclear cells. *Life Sci* 67:147-154, 2000
7. Christopher J, Orlando O, Robert A: Resolution of focal CT hypodense lesions in patients with Subarachnoid hemorrhage. *Surg Neurol* 39:158-162,1993
8. Clozel M, Watanebe H: BQ-123, a peptidic endothelin -a receptor antagonist, prevents the early cerebral vasospasm following subarachnoid hemorrhage after intracisternal but not intravenous injection. *Life Sciences*, 52:825-834, 1993
9. Cook DA, Vollrath B: Free radicals and intracellular events associated with cerebrovascular spasm. *Cardiovasc Res* 30:493-500, 1995
10. Dohrmann GJ: Choroid plexus: A historical review. *Brain Res* 18: 197-218, 1970
11. Drake MF: Cell death in the choroids plexus following transient forebrain global ischemia in the rat. *Microscopy Research and Technique* 52: 130-136, 2001
12. Ennis SR, Keep RF: The effects of cerebral ischemia on the rat choroid plexus. *J Cereb Blood Flow Metab* 26:675-683, 2006
13. Ferreira A, Braga FM: Microsurgical anatomy of the anterior choroidal artery. *Arq Neuropsiquiatr* 48:448-453, 1990
14. Gokce C, Gulsen S, Yilmaz C, Guven G, Caner H, Altinors N: The effect of thesildenafil citrate on cerebral vasospasm and apoptosis following experimental subarachnoid hemorrhage in rats. *J Neurosurg Sci* 54(1):29-37, 2010

15. Güney O, Erdi F, Esen H, Kiyici A, Kocaogullar Y: N-acetylcysteine prevents vasospasm after subarachnoid hemorrhage. *World Neurosurg* Jan; 73(1):42-49; discussion e3. Epub 2009 Aug 7, 2010
16. Hop JW, Rinkel GJ, Algra A, van Gijn J: Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. *Stroke* 28(3):660-664 Review, 1997
17. Hurst RW, Schnee C, Raps EC, Farber R, Flamm ES: Role of transcranial doppler in neuroradiological treatment of intracranial vasospasm *Stroke*, 24:299-303, 1993
18. Jan M, Buchheit F, Tremoulet M: Therapeutic trial of intravenous nimodipine in patients with established cerebral vasospasm after rupture of intracranial aneurysms. *Neurosurgery* 23: 154-157, 1998
19. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL: The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. *J Neurosurg* 73(1):18-36, 1990
20. Liebeskind DS, Hurst RW: Infarction of the Choroid Plexus. *AJNR Am J Neuroradiol* 25:289-290, 2004
21. McComb JG: Recent research into the nature of cerebrospinal fluid formation and absorption. *J Neurosurg*. 159(3):369-383, 1983
22. Medlock MD, Dulebohn SC, Elwood PW: Prophylactic hypervolemia without calcium channel blockers in early aneurysm surgery. *Neurosurgery* 30: 12-16, 1992
23. Origitano TC, Wascher TM, Reichman OH, Anderson DE: Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. *Neurosurgery* 27: 729-739, 1990
24. Pakarinen S: Incidence, aetiology, and prognosis of primary subarachnoid haemorrhage. A study based on 589 cases diagnosed in a defined urban population during a defined period. *Acta Neurol Scand* 43:Suppl 29:1-28, 1967
25. Timurkaynak E, Rhoton AL Jr, Barry M: Microsurgical anatomy and operative approaches to the lateral ventricles. *Neurosurgery* 19(5):685-723, 1986
26. Wolburg H, Paulus W: Choroid plexus: Biology and pathology *Acta Neuropathol* 119:75-88, 2010
27. Yasargil MG, Fox JL, Ray MW: The operative approach to aneurysms of the anterior communicating artery. *Microneurosurgery*, vol: 2. New York: Springer-Verlag, 1975:113-170