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ARAŞTIRMA / RESEARCH

Endothelin-1 levels in serum and cerebrospinal fluid after vasospasm following spontaneous subarachnoid hemorrhage

Spontan subaraknoid kanamayı takiben gelişen vazospazm sonrası serum ve serebrospinal sıvıda endotelin-1 düzeyleri

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Abstract

Purpose: The aim of the present study was to analyse endothelin-1 levels in serum and cerebrospinal fluid samples in patients with subarachnoid haemorrhage and evaluated the effects on vasospasm.

Materials and Methods: The patients were selected among those who referred to intensive care unit of neurosurgery department within several hours following subarachnoid haemorrhage. Subarachnoid haemorrhage was diagnosed through cerebral computed tomography and lumbar punction. First neurological examinations of the patients were evaluated according to Hunt-Hess classification and the blood quantity was detected by cerebral computed tomography according to Fisher classification.

Results: Serum and cerebrospinal fluid samples of 20 patients enrolled into the present study were collected at days 1, 3, 5, and 7 after subarachnoid haemorrhage.. According to Hunt-Hess classification, 6 patients were evaluated as Stage I, 10 patients as Stage II, 2 patients as Stage III and 2 patients as Stage IV. Seventeen patients were detected as Stage II whereas 3 patients were Stage IV according to Fisher classification. Vasospasm was detected in cases 3, 6, 11 and 18 by digital subtraction angiography.

Conclusion: As the Fisher and Hunt-Hess classifications increased, the risk of cerebral vasospasm increased. The present study revealed that endothelin-1 levels increase after subarachnoid haemorrhage. and Endothelin-1 particularly may play an important role in the vasospasm following spontaneous subarachnoid haemorrhage.

Keywords: Endothelin-1, subarachnoid haemorrhage, vasospasm

Öz

Amaç: Bu çalışmanın amacı subaraknoid kanamalı hastalarda serum ve beyin omurilik sıvısı örneklerinde endotelin-1 düzeylerini analiz etmek ve vazospazm üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntem: Hastalar subaraknoid kanamayı takiben birkaç saat içinde beyin cerrahisi bölümünün yoğun bakım ünitesine yatırılan hastalar arasından seçildi. Subaraknoid kanama teşhisi serebral bilgisayarlı tomografi ve lomber ponksiyon ile konuldu. Hastaların ilk nörolojik muayeneleri Hunt-Hess sınıflamasına göre değerlendirildi ve serebral bilgisayarlı tomografi ile tespit edilen kan miktarları Fisher sınıflamasına göre derecelendirildi.

Bulgular: Çalışmaya dahil edilen 20 hastanın serum ve beyin omurilik sıvısı örnekleri subaraknoid kanamanın ardından 1, 3, 5 ve 7. günlerde toplandı. Hunt-Hess sınıflamasına göre; 6 hasta Evre I, 10 hasta Evre II, 2 hasta Evre III ve 2 hasta Evre IV olarak değerlendirildi. Fisher sınıflamasına göre; 17 hasta Evre II, 3 hasta Evre IV olarak saptandı. Vasospazm, 3, 6, 11 ve 18 numaralı olgularda dijital subtraksiyon anjiyografi ile tespit edildi.

Sonuç: Yaptığımız çalışmada, Fisher ve Hunt-Hess sınıflandırmalarında evre arttıkça serebral vazospazm riskinin arttığı saptanmıştır. Ayrıca endotelin-1 düzeylerinin subaraknoid kanamadan sonra arttığı ve artan endotelin-1 seviyelerinin spontan subaraknoid kanamayı takiben vazospazmda önemli bir rol oynayabileceği ortaya konmuştur.

Anahtar kelimeler: Endotelin-1, subaraknoid kanama, vazospazm

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INTRODUCTION

Cerebral vasospasm is one of the most serious complications following spontaneous subarachnoid hemorrhage (SAH). The incidence of angiographic vasospasm reach up to 50% whereas it is detected in about 30% of the patients with symptomatic vasospasm[1,2]. A progression to cerebral infarction is detected in 50% of the symptomatic cases[3,4]. Because of such high rate of morbidity, the research studies focus on identification of the vasospasm mechanism and determination of the risk factors.

Endothelin-1 (ET-1) was first defined as a strong vasoconstrictor peptide originated from the endothelium[5,6]. Then, different pharmacological effects of endothelin were shown on many tissues within and out of the cardiovascular system. An association between cerebral vasospasm (CV) appeared after subarachnoid haemorrhage and ET-1 is considered and different studies are conducted for this purpose[4,6-8]. The present study analysed ET-1 levels in serum and cerebrospinal fluid (CSF) samples of 20 patients with SAH and evaluated the effects on vasospasm.

MATERIALS AND METHODS

The present clinical study was conducted on 20 patients who were admitted to intensive care unit by diagnosis of spontaneous subarachnoid hemorrhage and monitored in Neurosurgery Department of Cukurova University, Faculty of Medicine. Ethics committee approval was received for this study from the ethics committee of Cukurova University (2 / 12.02.2008). Written informed consents were obtained from patients and the parents of the patients/patient who participated in this study. The patients were selected among those who referred to our clinic within several hours following onset of the symptoms related to subarachnoid hemorrhage. First neurological examinations were evaluated according to Hunt-Hess subarachnoid haemorrhage classification. Subarachnoid hemorrhage was detected through cerebral computed tomography (CCT) and lumbar punction (LP). The Fisher's classification system was used to demonstrate the association between the blood quantity in CCT and the risk of vasospasm in the patients.

Routine haemogram (erythrocyte, leukocyte, haemoglobin, hematocrite), blood glucose levels, ionogram (sodium, potassium, chloride, BUN, calcium, creatinin), hepatic function tests, haemorrhagic diathesis tests and electrocardiography were performed. Vital signs of the patients who were admitted to the intensive care unit of neurosurgery department were monitored frequently. Analgesic, sedative, anti-edema, laxative, antihypertensive treatments were implemented individually or in combination. Digital subtraction angiography (DSA) was performed on the patients whose clinical findings were compliant.

Ten individuals without any vascular diseases, nervous system trauma or inflammatory disease were enrolled into the study as the control group. CSF and serum samples were collected from the control group just once. ET-1 levels in serum and CSF samples collected from the patient and control groups were analysed through micro-ELISA method and the results were obtained. The association between neurological states, CCT findings, DSA findings as well as ET-1 levels in serum and CSF were evaluated statistically in the present study.

Statistical analysis

The SPSS 13.0 package program was used for statistical analysis of the data. Non-parametric Wilcoxon Signed Ranks test or Mann-Whitney U test was used for comparison of the continuous variables such as ET-1 levels. Ki-square was utilized to compare discrete variables such as staging. Somers'd test was used for evaluation of the correlation between such discrete variables. The statistical significance level of the tests was accepted as 0.05.

RESULTS

The patients included 13 males and 7 females. The age average was detected as 53.40 ± 8.51 (34-65). According to Hunt-Hess classification, 6 patients were evaluated as Stage I (SI), 10 patients were SII, 2 patients were SIII and 2 patients were SIV. Seventeen patients were SII (85%) whereas 3 patients were SIV (15%) according to Fisher classification.

Deterioration of neurological condition occurred in 5 patients. Neurological presentation became worse in first case (case 2) at day 2 of admission. The patient progressed from SII to SV. No re-hemorrhage was detected in the CCT. However,

there was an imaging finding compliant to an infarction zone on the temporoparietal area on the right. DSA could not be done. The patient died at day 9. The second case worsening (case 4) appeared at day 3 of admission. The patient progressed from SII to SV. No re-haemorrhage was detected by CCT. An imaging finding consistent with infarction was detected in frontoparietal zone bilaterally. DSA could not be done. The patient died at day 10. The third case worsening (case 5) appeared at day 2 of admission. The patient progressed from SII to SIV according to Hunt-Hess classification. An imaging finding compliant to cerebral infarction was detected in CCT. DSA was performed. The patient whom no vascular pathology was detected in cerebral angiography was referred to Neurology department. The fourth patient (case 10) progressed from SII to SIII at day 1. A re-hemorrhage was detected in the CCT. DSA was performed. Saccular aneurysm was detected in the right internal carotid artery. No vasospasm existed. Aneurysm surgery was performed. The patient was discharged after cured. Neurological presentation of the fifth patient (case 12) became worse at day 3. The patient progressed from SII to SV. A re-hemorrhage was detected in the CCT. Urgent intracerebral hematoma surgery was implemented. DSA could not be done; the patient died at day 8.

Table 1. Clinical characteristics 20 patients with spontaneous subarachnoid haemorrhage.

Patient	Age/Gender	Etiology of SAH	Hunt-Hess grading	Fisher grading	Vasospasm	Conclusion
1	55/F	Left middle cerebral artery aneurysm	S2	S2	-	Operated/ Discharged
2	50/F	DSA could not be done	S2-S5	S2	-	Exitus
3	34/M	Basilar apex aneurysm	S4	S4	+	Exitus
4	59/M	DSA could not be done	S2-S5	S2	-	Exitus
5	61/F	DSA no pathology	S2-S4	S2	-	Referred
6	57/F	Anterior communicating artery aneurysm	S4	S4	+	Exitus
7	65/F	DSA no pathology	S1	S2	-	Referred
8	53/M	Right middle cerebral artery aneurysm	S2	S2	-	Operated/ Discharged
9	56/M	DSA no pathology	S1	S2	-	Referred
10	44/M	Right internal carotid artery aneurysm	S2-S3	S2	-	Operated/ Discharged
11	45/M	Right middle cerebral artery aneurysm	S3	S4	+	Exitus
12	62/M	DSA could not be done	S1-S5	S2	-	Exitus
13	64/M	Left internal carotid artery aneurysm	S2	S2	-	Operated/ Discharged
14	60/M	Left middle cerebral artery aneurysm	S2	S2	-	Operated/ Discharged
15	58/M	DSA no pathology	S1	S2	-	Referred
16	52/M	Right middle cerebral artery aneurysm	S1	S2	-	Operated/ Discharged
17	58/M	Anterior communicating artery aneurysm	S1	S2	-	Operated/ Discharged
18	48/F	Left internal carotid artery aneurysm	S3	S2	+	Operated/ Discharged
19	50/F	Left middle cerebral artery aneurysm	S2	S2	-	Operated/ Discharged
20	37/M	Right middle cerebral artery aneurysm	S2	S2	-	Operated/ Discharged

SAH: Subarachnoid haemorrhage, DSA: Digital subtraction angiography

Table 2. Serum and CSF ET-1 levels after subarachnoid haemorrhage.

	Vasospasm (+)		Vasospasm (-)	
CSF ET-1	N	Mean standard deviation/Min/Max	N	Mean SD Min/Max
ET-1 - Day 1	20	0.01/0/0.01/0.01	20	0.01/0/0.01/0.01
ET-1 - Day 3	20	0.18/0.59/0.01/2.6	20	0.11/0.41/0.01/1.8
ET-1 - Day 5	20	0.7/1.79/0.01/6.7	20	0.13/0.44/0.01/1.9
ET-1 - Day 7	20	1.19/3.12/0.01/10	20	0.15/0.51/0.01/2.1
	Vasospasm (+)		Vasospasm (-)	
Serum ET-1	N	Mean standard deviation/Min/Max	N	Mean SD Min/Max
ET-1 - Day 1	20	0.01/0/0.01/0.01	20	0.01/0/0.01/0.01
ET-1 - Day 3	20	0.08/0.2/0.01/0.8	20	0.08/0.33/0.01/1.2
ET-1 - Day 5	20	0.39/1.16/0.01/4.6	20	0.1/0.36/0.01/1.4
ET-1 - Day 7	20	1.06/3.06/0.01/10	20	0.14/0.45/0.01/1.9

CSF: Cerebrospinal fluid, ET-1: Endothelin-1

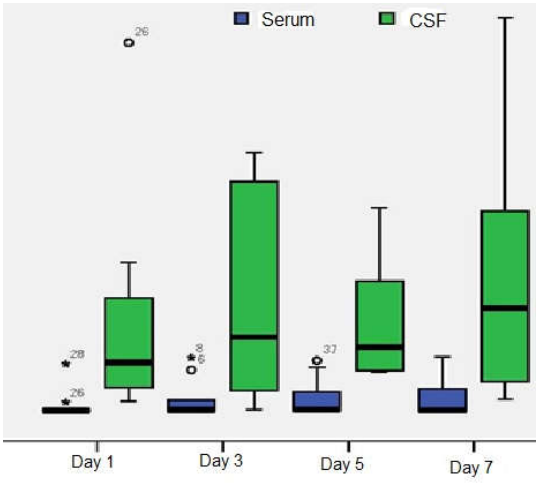

Figure 1. A comparison of serum and CSF ET-1 levels after subarachnoid haemorrhage.

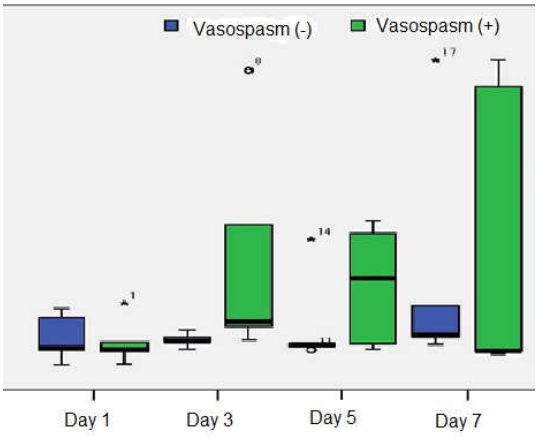

Figure 2. The association of CSF ET-1 and vasospasm following subarachnoid haemorrhage.

DSA was performed on 17 patients. DSA could not be performed on 3 patients since clinical presentations were not compliant. Ten of the cases who had cerebral angiography were operated. Although subarachnoid haemorrhage was detected by CCT and LP in 4 patients of those who had DSA, no aneurysm was detected in the cerebral angiography. Three patients whose clinical and neurological states were poor died and cerebral angiography could not be performed for them; and 3 patients who had cerebral aneurysms and vasospasm were lost.

It was detected that probability of vasospasm increased by elevation of Hunt-Hess stage ($p < 0.05$). Similarly, probability of vasospasm development was detected increased by increase of Fisher stage ($p < 0.05$) (Table 1). ET-1 levels in CSF at days 1, 3, 5 and 7 following SAH were detected statistically higher than serum ET-1 levels (Figure 1). When the vasospasm following SAH was compared with serum ET-1 and CSF ET-1 levels, the risk of vasospasm development was detected to increase in the patients whose ET-1 level increased from day 5 as well as the patients whose CSF ET-1 levels increased from day 3 (Table 2, Figure 2).

DISCUSSION

Cerebral vasospasm may be defined as narrowing of the cerebral vascular tree. The leading cause of mortality and morbidity which affect the prognosis after SAH is the vasospasm and it is a fact that such condition is not treatable. The cerebral arterial

vasospasm may be focal, segmental, diffuse, symptomatic or asymptomatic. Late, focal or diffuse ischemic neurological deficits are together with -cerebral arterial vasospasm. Prominent symptoms of the vasospasm may develop slowly within hours, days. Severe headache, confusion, meningismus, subfebrile fever and focal neurological findings are prominent symptoms of the vasospasm[9-14].

Pathogenesis of the cerebral vasopasm has not been clarified yet. The blood within subarachnoid space play an important role in cerebral vasospasm. Vasospasm was considered to be associated with multifactorial cases such as vasodilatation-inhibiting agents which provide long term arterial contraction, proliferative vasculopathy, inflammatory events, mechanical effects, blood components (oxyhemoglobin, endothelins, iron, norepinephrine, prostaglandins, free radicals) and immuno-reactive process[10,14-17].

The bleeding appeared after rupture of the aneurysm causes an increase of pressure in subarachnoid space and tampons the aneurysm rupture and the haemorrhage stops. Platelet accumulation and white thrombus appear on the rupture site on the aneurysm wall. The platelets release serotonin and thromboxan A2 and cause vascular stenosis in the ruptured vessel. Fibrin accumulates on the white thrombus and red thrombus appear and obstructs the ruptured site. The spasm started at that zone may remain local or progress diffusely along the vessel[18-20]. The spasm started from the site close to the thrombus is usually detected on distal side of the internal carotid artery and proximal side of the mid-and anterior cerebral artery. Stenotic zones of the artery is resistant to the spasm more. Therefore, it may be detected as segmental. As the spasm is severe, it diffuses along all arteries. It may involve the contralateral hemisphere arteries. The spasm narrows the lumen by 50% or 90% in some cases and the prognosis is very poor[19-23]. Serotonin, histamine and prostoglandins are released from the platelets by onset of the coagulation process after SAH and early cerebral vasospasm starts. Chatecolamines loose their effects at the end of 24 hours and hemolysis in the erythrocytes start. Late cerebral vasospasm starts as a result of blood products and lipid peroxidation. The disruption in the vascular endothelial ells increases the spasm more[14-17]. Endothelins are a family consisting of 3 vasoconstrictor iso-peptides (ET-1, ET-2, ET-3) and expressed from different cell types of the brain including neurons, glial cells and macrophages. The experimental studies showed that ET-1 presents a strong and long-term vasoconstrictor effect which cause morphological changes related to late term cerebral vasospasm after SAH[24-28].

ET-1 concentration in serum and CSF samples of the patients with subarachnoid hemorrhage were analysed in some studies; however, the results are contradictory. Recent findings are considered that ET-1 play a role in cerebral vasospasm in human[24,29-31]. Some animal studies conducted showed that ET-1 antagonists cured the cerebral vasospasm[32-35]. The studies where the association between ET-1 and cerebral ischemia were evaluated, CSF ET-1 levels were detected as increased in cerebral infarction[29,35-38].

Suzuki et al.[6] detected in their clinical study that among 30 patients whose serum and CSF samples were collected after SAH, 18 had cerebral vasospasm detected clinically whereas 10 patients developed angiographic vasospasm. CSF ET-1 levels were measured up to day 18 following the bleeding; basal CSF level significantly increased up to day 6 and then progressively decreased and it was shown that ET-1 exists with a high concentration in CSF when compared with the control group.

Masaoka et al.[39] detected that plasma ET-1 levels started to increase at day 3 of symptomatic vasospasm and reached to the peak level at day 7 in the patients with aneurysmal SAH. This was associated with production of endogenous ET-1 by the authors. In a study performed by Mascia et al.[4], serum and CSF ET-1 levels of 20 patients with SAH were measured; ET-1 concentrations were detected higher in the patients whom vasospasm was detected.

In the study conducted by Clozel et al.[27], efficiency of BQ123 (potent antagonist of endothelin-A receptor) was analysed; and it was demonstrated that such agent prevented development of cerebral vasospasm in the rat models. Matsumura et al.[34] used phosphoramidone, an endothelin antagonist on dog models with SAH in their study and detected that such agent prevented cerebral vasospasm.

The present study revealed the results in line with the literature. When we analysed ET-1 levels of CSF and serum samples of those who developed cerebral vasospasm among 20 patients with SAH, ET-1

levels were detected higher at days 3 and 5 after SAH when compared with the control group; and such level was detected over 10 pg/ml at day 7. There was not any significant difference shown when ET-1 concentration of the patients without vasospasm were compared with the control group. The risk of vasospasm was detected as increased in the patients whose CSF ET-1 level increased from day 3 and those whose serum ET-1 level increased from day 5.

In conclusion; different mechanisms of the immune system play a role as well as the vasospasm developed after SAH. The present clinical study concluded that ET-1 increase in CSF after SAH and it may be effective on development of vasospasm. Further clinical and experimental studies are needed to confirm the role of endothelins in vasospasm and to support these findings. Thus, medical therapy of this significant pathology which causes severe morbidity and mortality may be improved.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EB; Veri toplama: VA, GÇ, SKO; Veri analizi ve yorumlama: VA, GÇ, AA; Yazı taslağı: EB, KO; İçeriğin eleştirel incelenmesi: MT; Son onay ve sorumluluk: EB, KO, SKO, GÇ, VA, AA, MT; Teknik ve malzeme desteği: EB, AA, KO; Süpervizyon: MT; Fon sağlama (mevcut ise): yok.
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REFERENCES

1. Sundt TM Jr, Kobayashi S, Fode NC, Whisnant JP. Results and complications of surgical management of 809 intracranial aneurysms in 722 cases. Related and unrelated to grade of patient, type of aneurysm, andtiming of surgery. J Neurosurg. 1982;56:753-65.
2. 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. 1990;73:18-36.
3. Adams HP, Kassell NF, Torner JC, Haley EC Jr. Predicting cerebral ischemia after aneurysmal subarachnoid hemorrhage: influences of clinical condition, CT results and fibrinolytic therapy: a report of the Cooperative Aneurysm Study. Neurology. 1987;37:1586-91.
4. Mascia L, Fedorko L, Stewart DJ, Mohamed F, terBrugge K, Ranieri VM et al. Temporal relationship between endothelin-1 concentrations and cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2001;32:1185-93.
5. Ando K, Hirata Y, Togashi K, Kawamaki M, Maruno F. Endothelin-1 and endothelin-3-like immunoreactivity in human cerebrospinal fluid. J Cardiovascular Pharmacology. 1991;17:434-6.
6. Suzuki R, Masaoka E, Hirata H, Marumo F, Isotani E, Hirakawa K. The role of endothelin-1 in the origin of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg. 1992;77:96-100.
7. Bellapart J, Jones L, Bandeshe H, Boots R. Plasma endothelin-1 as screening marker for cerebral vasospasm after subarachnoid hemorrhage. Neurocrit Care. 2014;20:77-83.
8. Kessler IM, Pacheco YM, Lozzi SP, de Araujo AS Jr, Onishi FJ, de Mello PA. Endothelin-1 levels in plasma and cerebrospinal fluid of patients with cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Surg Neurol. 2005;64:2-5.
9. Munakata A, Naraoka M, Katagai T, Shimamura N, Ohkuma H. Role of cyclooxygenase-2 in relation to nitric oxide and endothelin-1 on pathogenesis of cerebral vasospasm after subarachnoid hemorrhage in rabbit. Transl Stroke Res. 2016;7:220-7.
10. Bickford JS, Ali NF, Nick JA, Al-Yahia M, Beachy DE, Dore S et al. Endothelin-1-mediated vasoconstriction alters cerebral gene expression in iron homeostasis and eicosanoid metabolism. Brain Res. 2014;1588:25-36.
11. Cengiz SL, Erdi MF, Tosun M, Atalik E, Avunduk MC, Sönmez FC et al. Beneficial effects of levosimendan on cerebral vasospasm induced by subarachnoid haemorrhage: An experimental study. Brain Inj. 2010;24:877-85.
12. Heros RC, Zervas NT, Varsos V. Cerebral vasospasm after SAH. An update. Ann Neurology. 1983;14:599-608.
13. Knekt P, Reunanen A, Ahok A. Risk factors for SAH in a longitudinal population study. J Clin Epidemiology. 1991;44:933-9.
14. Penn DL, Witte SR, Komotar RJ, Sander Connolly E Jr. Pathological mechanisms underlying aneurysmal subarachnoid haemorrhage and vasospasm. J Clin Neurosci. 2015;22:1-5.
15. Saveland H, Sonesson B, Lujungren B. Outcome evaluation following SAH. J Neurosurg. 1986;4:191-5.
16. Wilkins RH. Cerebral vazospasm. Contemporary. Neurosurgery. 1988:10:18-21.
17. Wirth FP. Surgical treatment of incidental intracranial aneurysms. Clin Neurosurg. 1986;33:125-35.

18. Ecker A, Riemenschenider PA. Arteriographic demonstration of spazm of the intracranial arteries. J Neurosurg. 1951;8:660-7.
19. Griessenauer CJ, Starke RM, Foreman PM, Hendrix P, Harrigan MR, Fisher WS 3rd et al. Associations between endothelin polymorphisms and aneurysmal subarachnoid hemorrhage, clinical vasospasm, delayed cerebral ischemia, and functional outcome. J Neurosurg. 2017;26:1-7.
20. Tıt M, Birger A, Annika L, Hans VH. Increased interleukin-6 levels in cerebrospinal fluid following subarachnoid hemorrahage. J Neurosurg. 1993;78:562-7.
21. Gaetani P, Rodriguez y Baena R, Grignani G, Spanu G, Pacchiarini L, Paoletti P. Endothelin and aneurysmal subarachnoid haemorrhage: a study of subarachnoid cisternal cerebrospinal fluid. J Neurol Neurosurg Pschiatry. 1994;57:66-72.
22. Gaetani P, Tartara F, Pignatti P, Tancioni F, Rodriguez y Baena R, De Benedetti F. Cisternal CSF levels of cytokines after subarachnoid hemorrhage. Neurol Res. 1998;20:337-42.
23. Suzuki K, Meguro K, Sakurai T, Saitoh Y, Takeuchi S, Nose T. Endothelin-1 concentration increases in the cerebrospinal fluid in cerebral vasospasm caused by subarachnoid hemorrhage. Surg Neurol. 2000;53:131-5.
24. Seifert V, Loffler B, Zimmermann M, Roux S, Stolke D. Endothelin concentrations in patients with aneurysmal subarachnoid hemorrhage: correlation with cerebral vasospasm, delayed ischemic neurological deficits and volume of hematoma. J Neurosurg. 1995;82:55-62.
25. Ohlstein E, Storer B. Oxyhemoglobin stimulation of endothelin production in cultured endothelial cells. J Neurosurg. 1992;77:274-8.
26. Gallek MJ, Alexander SA, Crago E, Sherwood PR, Klamerus M, Horowitz MB et al. Endothelin-1 gene polymorphisms influence cerebrospinal fluid endothelin-1 levels following aneurysmal subarachnoid hemorrhage. Biol Res Nurs. 2015;17(2):185-90.
27. Clozel M, Breu V, Burri K, Cassal JM, Fischli W, Gray GA et al. Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist. Nature. 1993;365:759-61.
28. Lei Q, Li S, Zheng R, Xu K, Li S. Endothelin-1 expression and alterations of cerebral microcirculation after experimental subarachnoid hemorrhage. Neuroradiology. 2015;57:63-70.
29. Rosalind Lai PM, Du R. Role of genetic polymorphisms in predicting delayed cerebral ischemia and radiographic vasospasm after aneurysmal subarachnoid hemorrhage: a metaanalysis. World Neurosurg. 2015;84:933-41.
30. Shirakami G, Magaribuchi T, Shingu K, Kim S, Saito Y, Nakao K et al. Change of endothelin concentration in cerebrospinal fluid and plasma of patients with aneurysmal subarachnoid hemorrhage. Acta Anaesthesiol Scand. 1994;38:457-61.
31. Zimmermann M. Endothelin in cerebral vasospasm. Clinical and experimental results. J Neurosurg Sci. 1997;41:139-51.
32. Clyde BL, Resnick DK, Yonas H, Smith HA, Kaufmann AM. The relationship of blood velocity as measured by transcranial doppler ultrasonography to cerebral blood flow as determined by stable xenon computed tomographic studies after aneurysmal subarachnoid hemorrhage. Neurosurgery. 1996;38:896-905.
33. Itoh S, Sasaki T, Asai A, Kuchino Y. Prevention of delayed vasospasm by an endothelin ET-A receptor antagonist, BQ-123: change of ET-A receptor mRNA expression in a canine subarachnoid hemorrhage model. J Neurosurg. 1994;81:759-64.
34. Matsumura Y, Ikegawa R, Suzuki Y, Takaoka M, Uchida T, Kido H et al. Phosphoramidon prevents cerebral vasospasm following subarachnoid hemorrhage in dogs: the relationship to endothelin-1 levels in the cerebrospinal fluid. Life Sci. 1991;49:841-8.
35. Shigeno T, Clozel M, Sakai S, Saito A, Goto K. The effect of bosentan, a new potent endothelin receptor antagonist, on the pathogenesis of cerebral vasospasm. Neurosurg. 1995;37:87-90.
36. Armstead WN. Role of endothelin in pial artery vasoconstriction and altered responses to vasopressin after brain injury. J Neurosurg. 1996;85:901-7.
37. Barone FC, Globus MY, Price WJ, White RF, Storer BL, Feuerstein GZ et al. Endothelin levels increase in rat focal and global ischemia. J Cereb Blood Flow Metab. 1994;14:337-42.
38. Lampl Y, Fleminger G, Gilad R, Galron R, Sarova PI, Sokolovsky M. Endothelin in cerebrospinal fluid and plasma of patients in the early stage of ischemic stroke. Stroke. 1997;28:1951-5.
39. Masaoka H, Suzuki R, Hirata Y. Raised plasma endothelin in aneurysmal subarachnoid hemorrhage. Lancet. 1989;82:1402.