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Evaluation of The Effect of Spinal Cord Electric Stimulation on Cerebral Vasospasm Using Hmpao Brain Spect

Omurilik Elektriksel Uyarımının Serebral Vazospazma Etkisinin Hmpao Beyin Spect ile Değerlendirilmesi

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ABSTRACT: ***Aim:*** In this study, we tried to show the experimental vasospasm produced in the rabbits and the effect of cervical spinal cord stimulation on vasospasm by using HMPAO brain perfusion SPECT.

Materials and methods: Thirtythree New-Zelland rabbits weighting 1500-2000 grams were used in our study. We divided them into three groups, each including 11 rabbits. In group 1, we produced only vasospasm. In group 2, only cervical spinal cord stimulation was performed. In group 3, we applied cervical spinal cord stimulation to the rabbits with cerebral vasospasm. HMPAO brain perfusion SPECT was performed all rabbits.

Results: In group 1, a decrease in perfusion was observed in HMPAO brain perfusion SPECT before and after cerebral vasospasm. In group 2, an increase in cerebral perfusion was observed before and after stimulation HMPAO brain perfusion SPECT. In group 3, before and after vasospazm+stimulation, HMPAO brain perfusion SPECT findings showed no difference in cerebral perfusion.

Conclusion: The results showed that the stimulation of the cervical spinal cord was not adequate in the treatment of cerebral vasospasm produced in the rabbits ($p>0.05$).

Key Words: SAH, cerebral vasospasm, cervical spinal cord stimulation, HMPAO brain SPECT.

ÖZET: ***Amaç:*** Bu çalışmada tavşanlarda deneysel olarak oluşturulan vasospazm ve vasospazm üzerine servikal spinal kord stimulasyonun etkisini HMPAO beyin perfüzyon SPECT ile göstermeye çalıştık.

Gereç ve Yöntem: Bu çalışmada 1500-2000 kg. ağırlığında 33 adet New-Zelland cinsi tavşan kullanıldı. Her birinde 11 tavşan olmak üzere 3 gruba ayrıldı. Birinci gruptaki tavşanlara sadece serebral vazospazm oluşturuldu. İkinci gruptaki tavşanlara sadece servikal spinal kord stimülasyonu uygulandı. Üçüncü grupta ise serebral vazospazm oluşturulan tavşanlara servikal spinal kord stimülasyonu uygulandı. Tüm tavşanlara HMPAO beyin perfüzyon SPECT uygulandı.

Bulgular: Birinci grupta, vazospazm öncesi ve sonrası yapılan HMPAO beyin perfüzyon SPECT çalışmasında, vazospazm sonrasında serebral perfüzyonun azaldığı görüldü. İkinci grupta, servikal spinal kord stimülasyonu öncesi ve sonrası yapılan HMPAO beyin perfüzyon SPECT çalışmasında stimülasyonun etkisiyle serebral perfüzyonun arttığı görüldü. Üçüncü grupta, servikal spinal kord stimülasyonu+vazospazm öncesi ve sonrası yapılan HMPAO beyin perfüzyon SPECT çalışmasında serebral perfüzyonda değişiklik olmadığı görüldü.

Sonuç: Sonuçlar göstermiştir ki, SAK sonucu tavşanlarda oluşturulan vasospazmın tedavisinde servikal spinal kord stimulasyonu tek başına yeterli değildir ($P>0,05$).

Anahtar kelimeler: SAK, serebral vazospazm, servikal spinal kord stimülasyonu, HMPAO beyin SPECT.

INTRODUCTION

The most important cause influencing mortality and morbidity in the patients with subarachnoidal hemorrhage (SAH) is cerebral vasospasm (1). Pathophysiology of vasospasm is still unclear and the treatment is usually palliative (2,3,4). Medical treatment of vasospasm involves barbiturates, calcium channel antagonists (i.e. nimodipine), free radical scavenging drugs (i.e. vitamine E, barbiturate, mannitol etc.) and cervical spinal cord stimulation (3-5).

Cerebral angioghraphy is gold standart in diagnosis of vasospasm (4,6) and MRI (Magnetic Resonance İmaging), CT (Computed Tomography), Transcranial Doppler, cerebral perfusion SPECT (Single Photon Emission Computed Tomography) are known to be the other diagnostic methods (6,7).

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Brain perfusion SPECT has been used in diagnosis and to follow up of cerebrovascular diseases since early 1990's (7). ^{99m}Tc-HMPAO is the commonly used agent in determining regional blood flow differences by brain perfusion SPECT (8-11).

The innervation of cerebral arteries originates from superior cervical and trigeminal ganglia (12,13). Sympathetic innervation of cerebral arteries is dominant, although there is an interaction between sympathetic and parasympathetic innervation (13). Sympathetic system is activated in SAH patients against severe headache, fear and horror phenomenons. As a result the arterial pressure and cellular metabolism increase, coagulation quickens, and vasoconstruction begins as a result (13,14). The electrical stimulation of spinal cord (ESSC) is proposed to have vasodilatator effect by secreting vasoactive substances by inhibiting sympathetic activity in SAH cases (15,16).

In our study, we aimed to investigate the effect of ESSC on cerebral vasospasm in experimental vasopasm rabbit model using HMPAO brain perfusion SPECT.

MATERIALS AND METHOD

Thirtythree New-Zelland rabbits weighting 1500-2000 grams were used in our study. We divided them into three groups, each includes 11 rabbits. All of the rabbits were anesthetized using Xylazin HCl (Rompun 2%; 15mg/kg) and Ketamine HCl (Ketalar 25mg/kg). The physiologic atmosphere was performed by following up the arterial pressure, partial oxygen pressure and pulse parameters with CSI 508 Criticare non-invasive monitor. The rabbits were fixed on prone position, and total laminectomy was applied to first and second cervical vertebra throughout midline incision from protuberantia externa to caudal with a 1,5 cm diameter by passing through dermis, subdermis, facia and paravertebral muscles. Basal brain perfusion SPECT was performed before operation. 360° SPECT images were taken 20 minutes later, after 2-3 mCurie ^{99m}Tc-HMPAO I.V. injection, of each was consisted of 60 frames with 6° angles in 30 seconds by rotatable unicap gama camera with LEHR collimator fixed (PICKER PRISM 1500 model).

In group 1, non-heparinized autolog blood from ear artery (0.9 ml/kg) was injected to each cisterna magna of rabbits with PPD injector (1,17). Then the rabbits were performed upside down position for 20-25 minutes. HMPAO brain perfusion SPECT was performed on the fourth day after vasospasm with the same protocol.

In group 2, 0.1-0.2 cycles/second with 60-80 Hz stimulation was performed for 20 minutes to each rabbit by bipolar stimulator (radionics ojeman stimulator probe) in epidural space at posterior cervical spinal cord (18,19). HMPAO brain SPECT was performed immediality after stimulation.

In group 3, non-heparinized autolog blood from ear artery (0.9 ml/kg) was injected to each cisterna magna of rabbits with PPD injector. 0.1-0.2 cycles/second with 60-80 Hz stimulation was performed during 20 minutes to each rabbit by bipolar stimulator (radionics ojeman stimulator probe) in epidural space at posterior cervical spinal cord (18,19). Spinal cord stimulation was performed on the fourth day after vasospasm. HMPAO brain SPECT was performed immediality after stimulation.

The basal SPECT images were reconstructed and attenuation corrections were made by Wien filters. Coronal, sagittal and transverse sections were taken at 5,5 mm thickness. The four regions of interest (ROIs) as anterior-posterior and right-left cerebral regions on transverse images that were formated manually were analysed quantitatively (Figure I). Total count/pixels (c/p) ratio of all brain cortical areas was equalized to 100 to standardize the quantitative analysis results. Then each c/p ratios of ROIs were rated to total brain area c/p ratio.

All of the pre and post operational quantitative data were analysed by SPSS 6.0 Windows packet program. The mean and standart deviations of pre-post operational anterior-posterior and right-left brain areas c/p values were calculated (Table I). To analyse these data in each group Student's T test was used (Table II).

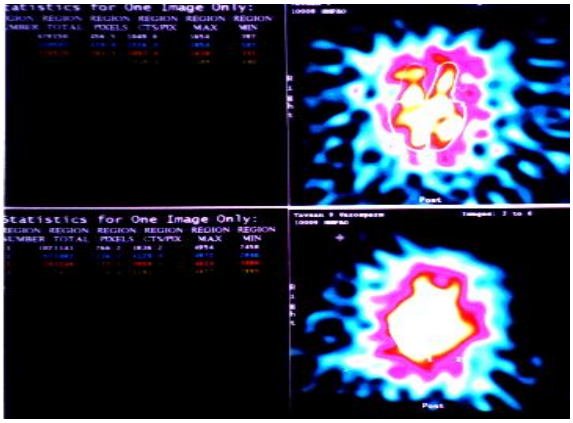

Figure 1. Transverse image of HMPAO brain SPECT in rabbit shows four regions of interest (ROIs) as anterior-posterior and right-left cerebral regions that were manually analysed

Table I: *Statistical mean and standard deviation values of anterior-posterior and right-left cerebral regions quantitative analysis (count/pixel) of all groups before and after application*

Type of Application	Grup I Mean/sd	Grup II Mean/sd	Grup III Mean/sd
Before Aplication			
Anterior	97,173 ± 4,629	97,127 ± 6,229	92,818± 8,105
Posterior	102,07 ± 3,457	102,84 ± 3,840	104,45± 4,714
Right	97,373 ± 1,008	99,809 ± 2,530	98,464± 2,536
Left	102,89 ± 1,050	100,15 ± 2,576	101,74± 2,951
After Aplication			
Anterior	98,773 ± 6,458	97,148 ± 5,691	98,645± 3,473
Posterior	100,98 ± 5,713	102,409 ± 4,275	101,11± 2,639
Right	99,427 ± 2,621	98,964 ± 2,417	100,28± 2,634
Left	100,71 ± 2,756	101,464 ± 2,259	99,764± 2,889

Table II: *Comparison of all groups mean c/p ratios and standard deviation of anterior-posterior and right-left cerebral regions before and after application.*

	Mean	sd	İSTATİSTİKSEL ANALİZ t	P
Before Aplication	97,173 - 102,07	± 4,629 ± 3,457		
GrupI Ant.- Post.	97,373 - 102,89	± 1,008 ± 1,050	*-2,813*	*,011*
Right- Left	97,127 - 102,84		*-12,57*	,000
GrupII Ant.- Post.	99,809 - 100,155	± 6,229 ± 3,840	*- 2,588*	,018
Right- Left		± 2,530 ± 2,576	*- ,317*	,754
GrupIII Ant.- Post.	92,818 - 104,45	± 8,105 ± 4,714	*- 4,116*	,001
Right- Left	98,464 - 101,74	± 2,536 ± 2,951	*- 2,790*	,001

		Mean	sd	İSTATİSTİKSEL ANALİZ t	P
After Aplication				*- ,850*	
GrupI	Ant.- Post.	98,773 100,98	± 6,458 ± 5,713	*- 1,118*	,406
	Right- Left	99,427 100,71	± 2,621 ± 2,756		,227
GrupII	Ant.- Post.	98,645 - 101,11	± 5,691 ± 4,275	*- 2,326*	,031
	Right- Left	100,28 - 99,764	± 2,417 ± 2,259	*- ,317*	,754
GrupIII	Ant.- Post.		± 3,473 ± 2,639	*- 1,873*	
	Right- Left	97,148 102,409	± 2,634 ± 2,889	*- ,440*	,076
		98,964 101,464			***,665***

RESULTS

The pre-operative c/p ratios of posterior and left cerebral regions were significantly higher in all groups when comparing anterior with posterior and right with left cerebral regions. Only, the c/p ratio difference between right and left cerebral regions was not statistically significant in group 2.

In group 1, c/p ratio of posterior cerebral region was statistically higher than anterior at the pre-vasospasmic phase (t:2,813, p<0,05). There was no significant difference between c/p ratios of anterior and posterior cerebral regions at the post-vasospasmic phase (p>0,05). The c/p ratio of left cerebral region was statistically higher than right at the pre-vasospasmic phase (t:12,572, p<0,05). There was no significant difference between c/p ratios of left and right cerebral regions at the post-vasospasmic phase (p>0,05).

In group 2, at the pre and post-stimulative phase c/p ratio of posterior was significantly higher than anterior cerebral region (t:2,588, p<0,05; t: 2,326, p<0,05, respectively). There was no significant differences between c/p ratios of left and right cerebral regions at the pre-stimulative phase (P>0,05). But, at the post stimulative phase c/p ratio of left cerebral region was significantly higher than the right (t: 2,506, p<0,05).

In group 3, at the pre-vasospasmic+stimulative phase c/p ratio of posterior cerebral region was significantly higher than anterior (t:4,116, p<0,05). There was no significant difference between c/p ratios of anterior and posterior cerebral regions at post-vasospasmic+stimulative phase (P>0,05). The left pre-vasospasmic+stimulative phase c/p ratio was significantly higher than the right cerebral region ratio (t:2,790, p<0,05). There was no significant difference in c/p ratio between left and right cerebral regions at the post-vasospasmic+stimulative phase (p>0,05).

DISCUSSION

One of the most important factors that effects mortality and morbidity in SAH patients is vasospasm (1,2). Vasospasm usually begin at the 3rd to 5th days of SAH and increase gradually in 2 to 4 weeks (1,2). Spasmogenic substances from subarachnoidal space, endothelial and inflammatory factors and immunohistochemical reactions are reported to play an important role in the pathophysiology of vasospasm (20). Cerebral blood flow (CBF) and cerebral blood volume (CBV) are found to be decreased as a result of vasospasm which means a decreas in cerebral perfusion (21).

Despite Digital Substraction Angiography (DSA) used is the gold standart method in the diagnosis of vasospasm, and is not frequently in clinical practice because of its invasive aspect (4,6,7). MRI, CT, Transcranial Doppler and ^{99m}Tc-HMPAO brain perfusion SPECT imaging methods are frequently preferable to DSA in the diagnosis of vasospasm (6,7). Brain perfusion SPECT imaging is wide spreadly used in diagnosis and follow up of cerebrovascular diseases (cerebral ischemia, transient ischemic attack, SAH, chronic vascular diseases and cerebrovascular dementia etc.) and brain death (9, 21-23).

Soucy J. P. et al (6), performed CT, angiography and ^{99m}Tc-HMPAO perfusion SPECT methods together in 15 SAH patients and they found a significant rCBF decrease in vasospasmic region and significant correlation between rCBF decrease and angiography findings. They revealed that brain perfusion SPECT is an effective method to detect rCBF changes in vasospasm patients.

Sympathetic innervation of cerebral arteries is known to be dominant physiologically, although there is an interaction between sympathetic and parasympathetic innervation (12-14). Pathophysiologic situations such as experimental SAH, increment in activation of sympathetic system, firstly. The increment in sympathetic activity causes vasoconstruction by α-1 adrenoreceptor and neurotransmitters. Experimental and clinical studies on vasoconstruction have been reported that sympathetic system may be inhibited by ESSC causing (functional reversible sympathetectomy), vasodilatation formates and the effects of vasospasm decrease due to inreases in rCBF (24-28).

In the light of other clinical and experimental studies, in the present study we aimed to detect the influences of ESSC on CBF using ^{99m}Tc-HMPAO brain perfusion SPECT in experimental SAH rabbit model.

Broseta et al. (19), in their clinical investigation, used CT, MRI, cerebral angiography and brain perfusion SPECT methods in 10 patients whose symptoms were likely and matched with ischemic lesions that have a decrease perfusion in SPECT study. Then stimulation has been applied to these patients for 19 months which were placed by local anaesthesia, and they have revealed that pre-stimulative hypoperfused regions in HMPAO perfusion SPECT improved to normal perfusion levels at post-stimulative phase. The neurological motor deficits did not improve significantly despite the positive post-stimulatory perfusion findings. In our study, in vasospasm group the difference in c/p ratios of posterior and left cerebral regions were found statistically significant at the pre-vasospasmic phase. Furthermore, these differences were not found to be significant after vasospasm. This finding showes that hypoperfusion due to vasospasm is more prominent in posterior and left regions.

Visocchi et al. (18), in their CBF evaluation study with ^{133}Xenon, were found 62% increase in rCBF after ESSC application using an electrode in cervical spinal epidural space of rabbits. Broseta et al.(19) in their experimental study, were performed bilateral internal carotid artery ligation to 15 rabbits, middle right cerebral artery microcoagulation to 15 rabbits and microcoagulation to vertebral artery at craniocervical junction in 15 rabbits. They have detected the decreases of CBF after microcoagulation as 65.6% in posterior fossa, 48.5% in right parietal 44.2% in left parietal and 35.7% in right frontal regions by replacing laser doppler flowmeter on bilateral frontal and parietal cortical areas. Then they were applied stimulation to C1-C2 vertebral junction of all subjects and observed 27% increase of blood flow in right frontal and parietal regions and 7% increase in contralateral side and 32% increase in posterior fossa. In the present study, in group 2 pre-stimulative c/p ratio of posterior cerebral region was significantly higher than anterior and this increase was found to be kept in the same level after stimulation. Post-stimulative c/p ratio in left cerebral region was significantly higher than right, although there was no significant difference in pre-stimulative phase. The stimulation is agreed to cause an increase CBF in left cerebral region.

Our preoperative vasospasm+stimulation group had same results as in vasospasm group. In group 2, we failed to show a significant increase in left cerebral region CBF after stimulation. Also we could not detect the effect of stimulation on vasospasm using HMPAO brain perfusion SPECT. Despite HMPAO brain perfusion SPECT has ability to inform us about regional brain perfusion, the quantitative evaluation of CBF (ml/100 gm tissue) could not be estimated exactly. This is the most important limitation of this study. ^{133}Xe and PET and (dynamic) doppler included 8 prope are used to estimate quantitative CBF changes (9,22,23). We consider that ^{133}Xe, PET and 8 prope (dynamic) Doppler combination with HMPAO brain perfusion SPECT would reveal overall data of the effect of vasospasm and stimulation on brain perfusion in experimental and clinical studies. Further multicentral studies are needed to search this subject.

The cerebral evaluations between groups did not support the differences in each group. We think that this finding is due to different operative applications, different data and the difficulties of HMPAO brain perfusion SPECT application in rabbits.

In conclusion, the findings of HMPAO brain perfusion SPECT in experimental pre and post-vasospasm, stimulation and vasospasm+stimulation, considered us that ESSC is insufficient alone in the treatment of vasospasm ($p>0,05$).

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