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Attenuation of Vasospasm by Dexmedetomidine after Experimental Subarachnoidal Haemorrhage in Rabbits*

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Aim: Vasospasm is one of the most important factors that influence the successful treatment of ruptured intracranial aneurysm. We studied if vasospasm following subarachnoidal haemorrhage (SAH) can be alleviated by dexmedetomidine in an animal model.

Materials and Methods: Experimental SAH was induced in 12 of 18 New Zealand rabbits by intracisternal injection of autologous blood. Control animals (sham SAH, n = 6) received intracisternal injection of the respective volume of physiological saline solution. Forty eight hours after the operation, rabbits in sham SAH and SAH-alone (n = 6) groups were infused intravenously with 0.9% sodium chloride for 2 h, whereas rabbits in SAH-dexmedetomidine group (n = 6) received intravenous infusion of 5 µg/kg per h dexmedetomidine for 2 h. All rabbits were sacrificed with penthotal 24 h after infusions. Basilar arteries were isolated and processed for histology.

Results: The histological specimens revealed evidence of arterial narrowing and vascular wall thickening in both SAH-alone and SAH-dexmedetomidine groups. The wall thickness of basilar artery significantly increased and lumen diameter significantly reduced in SAH-alone group in comparison with basilar arteries from other groups ($P < 0.05$). SAH-dexmedetomidine group revealed attenuation of vasospasm formed after 72 h.

Conclusions: Our study showed that vasospasm is attenuated by dexmedetomidine administered after vasospasm is formed in a rabbit model.

Key Words: Dexmedetomidine, subarachnoid haemorrhage, vasospasm.

Deneysel Subaraknoid Kanama Sonrası Oluşan Vazospazmın Dexmedetomidine ile Azaltılması

Amaç: Vazospazm kanamış intrakranyal anevrizmaların başarılı tedavisini etkileyen en önemli faktörlerden birisidir. Biz bu çalışmamızda subaraknoid kanama (SAK) sonrası gelişen vazospazmın dexmedetomidinle önlenip önlenemeyeceğini hayvan modelinde çalıştık.

Yöntem ve Gereç: On sekiz Yeni Zelanda tavşanının 12'sine kendi kanları intrasisternal şekilde verilerek deneysel SAK oluşturuldu. Kontrol grubundaki (Sham-SAK, n = 6) hayvanlara aynı miktarda fizyolojik salin solusyonu intrasisternal enjekte edildi. Operasyondan 48 saat sonra sham-SAK ve yalnız-SAK (n = 6) gruplarına intravenöz olarak 2 saat boyunca % 0,9 Sodyum Klor solüsyonu verildi. Yine operasyondan 48 saat sonra SAK-dexmedetomidine (n = 6) grubuna 2 saat süresince dexmedetomidine (saatte 5 µg/kg) verildi. Bu işlemlerden 24 saat sonra tüm hayvanlar pentotal infüzyonu sonrası sakrifiye edildi. Basilar arterleri çıkartıldı ve histolojik çalışma için hazırlandı.

Bulgular: Histolojik sonuçlar yalnız-SAK ve SAK-dexmedetomidine gruplarında arteryel daralma ve damar duvarında kalınlaşma gösterdi.Yalnız-SAK grubu diğer gruplar ile karşılaştırıldığında basilar arter duvar kalınlığı artması ve damar lumen çapının azalması istatiksel olarak anlamlıydı ($P < 0.05$). SAK-dexmedetomidine grubunda 72 saat sonra vazospazmın azaldığı gözlendi.

Sonuç: Bizim çalışmamız, tavşan modelinde vazospazm oluştukdan sonra dexmedetomidine uygulamanın vazospazmı azalttığını gösterdi.

Anahtar Sözcükler: Dexmedetomidine, subaraknoid kanama, vazospazm

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Introduction

Subarachnoid haemorrhage (SAH) is most commonly caused by a ruptured aneurysm in the circle of Willis. Vasospasm, occurring prior to, during, and after surgery (1), is one of the most important factors that influence successful treatment of ruptured intracranial aneurysm. Blood and blood breakdown products are considered as the important spasmogens in the etiology of vasospasm (2-7). A thickened hyperplastic arterial wall is also taken into consideration as a cause of vasospasm after SAH with a primary vascular spasm (2,3,6). It has been demonstrated that vasospasm can be influenced by many factors, among which the possible role of the sympathetic nervous system has been suggested (8).

Dexmedetomidine is recently used for sedation in the intensive care units. It inhibits central sympathetic discharge, decreases arterial blood pressure and heart rate and causes sedation due to its α_2 agonistic effects. Dexmedetomidine has also been reported to protect against incomplete ischemia in rats (9) and against focal ischemia in rabbits (10). Neuroprotection of dexmedetomidine is also shown in gerbil global ischemia model (11). However, it failed to protect against severe forebrain ischemia in rats (12). In these studies the effects of dexmedetomidine on cerebral vasculature were not reported.

Although another α_2 agonist, clonidine, has been shown to prevent chronic vasospasm (13), dexmedetomidine is not suggested for patients with SAH. In addition, since excessive sympathetic discharge is proposed as the cause of vasospasm and α_2 adrenoreceptor agonists have also been shown to reduce ischemic damage possibly by attenuating the excessive release of noradrenaline during energy failure (14), potential antivasospastic effect of dexmedetomidine is assumed. We aimed to study antivasospastic effect of dexmedetomidine after post-SAH vasospasm has developed, considering the fact that most of the patients are admitted to physicians after SAH has been established. We used rabbit SAH model because of the anatomical similarity of sympathetic innervation of rabbit cerebral arteries compared to human ones (15). In our study, we wanted to find out if vasospasm following subarachnoidal haemorrhage can be alleviated by dexmedetomidine.

Materials and Methods

This study was approved by the Animal Ethics Committee of Afyon Kocatepe University. One day before surgery, rabbits were fasted and pretreated with an antibiotic, cefazoline (Cefozin, 50 mg/kg, intravenously (I.V.), Bilim, Turkey).

The study was carried out on 18 male New Zealand rabbits (weighing 1500-2000 gr). Animals were anaesthetized with intramuscular (I.M.) Xylazine HCl (15mg/kg) / ketamine (25mg/kg), and placed on a heated surgical table to maintain body temperature at 37 ºC. After anesthesia, 2 L/min of oxygen was given to avoid hypoxia. Rabbits were randomly enrolled into 1 of the 3 groups: sham-SAH (n = 6), SAH-alone (n = 6), and SAH-dexmedetomidine (n = 6) group. All rabbits were fixed in a prone position and a midline incision between the ears over the external occipital protuberance was made caudally to reach cisterna magna. After the first incision, dermal and subdermal tissues, fascia and paravertebral muscles were dissected. The atlanto-occipital membrane was dissected and a 27-gauge needle was inserted through the dura and the arachnoid membrane into the cisterna magna. In the control group 0.9 ml/kg of 0.9% NaCl was given into cerebrospinal fluid (CSF). In 2 SAH groups, nonheparinized arterial blood (0.9 ml/kg) obtained from the ear artery was injected into the cisterna magna. In order to permit a good distribution of the blood around the basal intracranial arteries, rabbit was kept in a head down position from the onset of the injection until 10 min after injection. This procedure is similar to the method of Solomon et al. (16). After rabbits recovered from anesthesia, they were left for 48 h in their cages for the establishment of vasospasm.

After 48 h, all rabbits were reanesthetized with I.M. Xylazine HCl (15mg/kg) / ketamine (25mg/kg) and placed on a heated surgical table to maintain body temperature at 37 ºC. After anesthesia was introduced, 2 L/min of oxygen was given. Half of the initial dose of anesthetics was given to maintain anesthesia when the rabbits were starting to move or their heart beat increased by 10%. One of the ear arteries was cannulated to monitor arterial blood pressure and one of the ear veins was cannulated for intravenous fluid infusion. Electrocardiography, arterial blood pressure, peripheral oxygen saturation, and body temperature were monitored (Datex Ohmeda Type F-CU8, Helsinki, Finland) throughout the procedure. Control and SAH-alone group received I.V. infusion of 5

mL/kg of 0.9% NaCl per hour for 2 h, whereas SAH-dexmedetomidine group received 5μg/kg dexmedetomidine per hour as an I.V. infusion for 2 h. Total dose of 10 μg/kg of dexmedetomidine was infused in 0.9% NaCl at a rate of 5 mL/kg per hour (17).

All rabbits were sacrificed with 20 mg/kg penthotal after 24 h following the infusions, i.e. 72 h after SAH. Their brains were removed immediately for the histopathological study.

Histopathological examination

The samples were collected by cutting the brainstem including basilar artery and examined by a pathologist who was blinded to the study groups. Basilar arteries were harvested from the midline between basilar-posterior cerebral artery junction and basilar-vertebral artery junction and fixed in 10% neutral formalin solution. After dehydration procedures, the samples were embedded in paraffin; 4–6 μm sections were cut with a microtome and stained with hematoxylin and eosin (H&E). Mounted slides were evaluated and photographed using a light microscope (Olympus BX51, Tokyo, Japan).

Image analysis

The circumferences of internal elastic lamina and tunica adventitia of each basilar artery were marked and measured with an image analysis system. During marking the internal elastic lamina, the convolutions were included to the circumference of the basilar artery. The internal (lumen) and external diameters were calculated using mathematic formula for the measure of circumference. The wall thickness of the artery was calculated by subtraction of internal from external diameter. These measurements were made at 3 locations on the basilar artery; near the vertebrobasilar junction, at the midpoint, and close to the basilar tip. The wall thickness and lumen diameters were calculated for each vessel as the arithmetic mean of values obtained at these 3 locations.

The investigator who performed these measurements was blinded to the conditions. The system used is composed of a PC with hardware and software (Image-Pro Plus 5.0, Media Cybernetics, USA) for image acquisition and analysis, a Spot Insight QE (Diagnostic Instruments, USA) camera and an optical microscope. The method requires preliminary software procedures of spatial calibration (micron scale) and setting of color segmentation for quantitative color analysis.

Statistical Analysis

All data are presented as mean ± standard deviation (SD). Statistical analysis was performed on a personal computer using SPSS for Windows (SPSS Inc., USA). The data of physiological monitoring and histopathological images were considered to be nonparametric; therefore, they were treated using the Kruskal–Wallis H test analysis. The inter-group comparisons were performed using Mann–Whitney U tests. $P < 0.05$ was considered statistically significant.

Results

The histology of basilar arteries from 3 groups are shown in Figure 1. Light microscopy appearance of these arteries was normal in control group. The endothelium had a continuous monolayer overlying a thin convoluted internal elastic lamina (Figure 1a). In SAH-alone and SAH-dexmedetomidine groups, basilar arteries showed certain morphological changes such as increase of the intimal convolution, desquamation of the endothelial cells, and vacuolar degeneration of the tunica muscularis. There was also evidence of arterial narrowing and vascular wall thickening in both SAH-alone and SAH-dexmedetomidine groups (Figures 1b and 1c).

The luminal diameters and thickness of basilar arteries are shown in Table 1. The luminal diameters were 598 ± 15.3 μm, 346 ± 9.2 μm, and 553 ± 11.6 μm in control, SAH-alone, and SAH-dexmedetomidine groups, respectively. The luminal diameters of basilar arteries in SAH-alone group were significantly smaller than in control and SAH-dexmedetomidine groups ($P < 0.05$). The thickness of the basilar artery was 42 ± 1.2 μm, 54 ± 1.3 μm, and 40±1.1 μm in control, SAH-alone, and SAH-dexmedetomidine groups, respectively. Basilar artery wall thickness was significantly increased in SAH-alone group in comparison with the control and SAH-dexmedetomidine groups ($P < 0.05$).

There were no differences between the groups in the mean heart rhythm, mean arterial blood pressure, peripheral oxygen saturation, intracranial and body temperature measured during the study (Table 2).

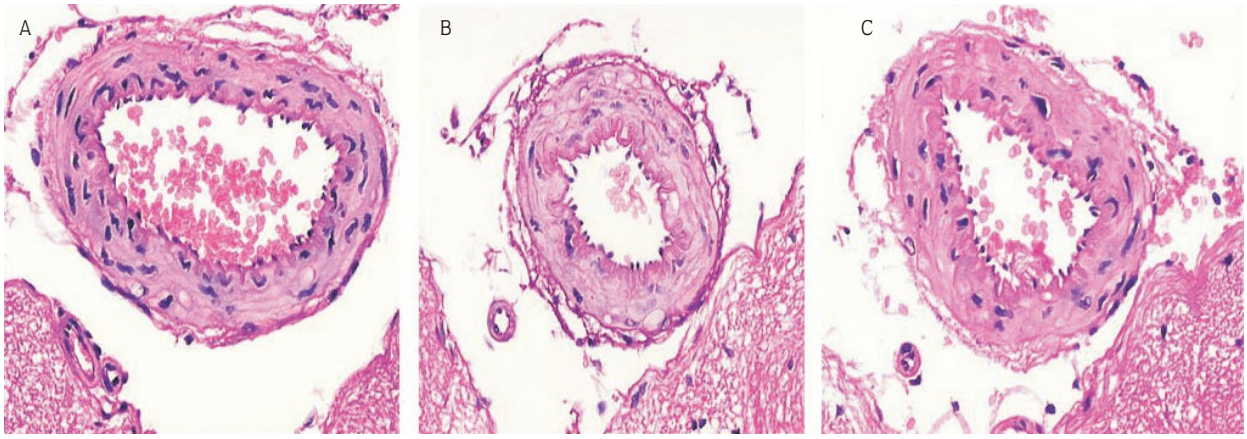

Figure 1. Cross section photograph of basillary arteries. A) Control group: Showing control basilar artery, a continuous monolayer of endothelium formed, overlying the thin convoluted smooth muscle cells surrounded the intima. H&E ×100. B) SAH-alone group: Significant degree of reduction in luminal diameter and increase in wall thickness is seen. H&E ×100. C) SAH-Dexmedetomidine group: The wall thickness and luminal diameter of the rat basilar arteries were increased compared to those in the SAH group. H&E ×100.

Table 1. Comparisons of wall thickness and luminal diameter of basilar artery in 3 groups. Values are represented as mean ± SD, and n = 6 for all groups (Mann-Whitney U Test).

Group	Diameter of basilar artery (μm)	Thickness of basilar artery (μm)
I- Control	598 ± 15.3	42 ± 1.2
II- SAH-alone	346 ± 9.2	54 ± 1.3
III- SAH-Dexmedetomidine	553 ± 11.6	40 ± 1.1
P values		
I-II	P < 0.05	P < 0.05
I-III	N.S.	N.S.
II-III	P < 0.05	P < 0.05

NS: Nonspecific (P > 0.05)

Discussion

The effects of dexmedetomidine on basilar artery after experimental SAH were studied by intracisternal injection of autologous blood in a rabbit model. Diameters of basilar artery were measured in fixed histological sections. Our data provide that selective α_2 adrenergic agonist, dexmedetomidine, may have antivasospastic effect in experimental SAH.

It is suggested that central sympathetic system is overstimulated and it also causes a stress response to the stressor after SAH. Following central sympathetic discharge, hypertension occurs and cell metabolism increases. Finally, stimulation of α-adrenoceptors causes vasospasm (15). Sympathetic stimulus that induces the formation of adrenaline and noradrenaline also causes abnormal sensitivity of the cerebral vasculature to increased catecholamines on arterial walls (18). Increased catecholamine levels were also suggested as the cause of degeneration that is seen in cerebral vascular system (18). Some researchers also suggest that plasma noradrenaline levels may be a reliable indicator of the outcome of vasospastic patients after SAH (19). There are also some reports demonstrating advantageous systemic and cerebral effects of α and β receptor blockade after subarachnoid haemorrhage (20).

Table 2: Physiological parameters of the groups.

	Times (minute)	MHR / minute	MAP	SaO_2	ICT	BT
Group I	0-30	170±0.5	80.2±0.3	98.1±0.2	36.5±0.01	36.5±0.02
	30-60	151±0.3	76.2±0.4	98.4±0.3	36.6±0.01	36.5±0.01
	60-90	150±0.6	74.3±0.2	98.6±0.2	36.5±0.03	36.6±0.02
	90-120	152±0.8	75.4±0.6	99.1±0.2	36.6±0.02	36.7±0.02
Group II	0-30	172±0.4	81.5±0.4	97.4±0.2	36.5±0.02	36.5±0.03
	30-60	152±0.3	78.4±0.6	98.1±0.1	36.5±0.03	36.6±0.01
	60-90	154±0.6	77.3±0.3	98.2±0.2	36.6±0.01	36.6±0.02
	90-120	153±0.5	78.3±0.5	98.6±0.3	36.6±0.02	36.6±0.03
Group III	0-30	169±0.7	75.2±0.5	98.0±0.1	36.5±0.02	36.5±0.01
	30-60	148±0.3	74.5±0.4	98.2±0.3	36.5±0.03	36.6±0.02
	60-90	150±0.8	73.5±0.5	98.5±0.3	36.6±0.03	36.6±0.01
	90-120	152±0.5	74.2±0.2	99.0±0.1	36.6±0.01	36.7±0.02

MHR, mean heart rhythm; MAP, mean arterial pressure (mmHg); SaO2, Oxygen saturation (%); ICT, intracranial temperature (°C); BT, body temperature (°C)

Participation of increased discharge of peripheral sympathetic nerve endings in delayed vasospasm after SAH was also suggested by Bunc et al. (21). This study demonstrated that exclusion of the peripheral sympathetic nervous system (upper gangliectomy), on the one hand, and of the systemic sympathetic nervous system (α-blocker phenoxybenzamine), on the other, was also effective in preventing vasospasm in the same SAH model (21).

$Alpha_2$ agonist clonidine showed its antivasospastic effect due to the blockade of the central noradrenergic discharge in conjunction with peripheral sympathetic inhibition (13). Sympathetic discharge blockade by clonidine has been demonstrated to effectively prevent chronic vasospasm in an experimental study (13). However, the clinical study of α_2 agonist clonidine showed that plasma noradrenaline levels were not affected by intravenous infusion in SAH patients (22). Lambert et al. (22) also suggested that lack of response to clonidine may be due to the route of administration, the dose of the drug, or the patient group studied.

$Alpha_2$ adrenergic receptors are widely distributed within the cerebral vasculature, and it has been proposed that specific cerebral vasoconstrictor responses are induced by activation of these receptors (23). Accordingly, dexmedetomidine decreased cerebral blood flow in both isoflurane- and halothane-anesthetized dogs without influencing the metabolic rate for oxygen (24,25). Moreover, it was also demonstrated that dexmedetomidine constricted cerebral vessels in pentobarbital-anesthetized dogs (26).

Prielipp et al. (27) showed that dexmedetomidine-induced sedation in young, healthy, normotensive volunteers is associated with the decrease of regional and global cerebral blood flow. However, it is unclear whether the same findings will be seen in hypertensive, older, and anesthetized patients, patients with traumatic brain injury, or patients with other intracranial or metabolic alterations of cerebral autoregulation. In an in vitro study, Bryan et al. (28) demonstrated α_2 adrenergic receptor-mediated dilation of rat middle cerebral arteries that involved NO and a pertussis toxin sensitive G protein as mediators.

NO level decreases in the first hour after SAH and the half-life reduces because of the oxidative stress. In the following hours, overproduction of NO results in overconsumption, and this process activates the production of free radicals (29). Additionally, excessive noradrenaline release after SAH has a potential role in the formation of free radicals (21). Dexmedetomidine may

inhibit the excessive catecholamine release via activating the presynaptic α-2 adrenoceptors and also may inhibit the formation of free radicals and oxidative stress after SAH.

According to the study of Kovacic et al. (30) and biphasic vasospasm model, the vasospasm increased at the 48th hour and between days 5 and 8. We administered dexmedetomidine at the 48th hour after SAH. Although, functional changes are seen earlier in vasospastic arteries, this preliminary study is based on morphological results. The morphological results of our study showed that the wall of basilar arteries were normal in control group. However, in SAH-alone and SAH-dexmedetomidine groups, the effect of vasospasm was seen in the wall of basilar arteries.

There was also evidence of arterial narrowing and vascular wall thickening (Figure 1b and 1c). Many conflicting results in dexmedetomidine induced recovery of SAH may suggest that peripheral sympathetic blockade is more important than central sympathetic blockade. Our results that showed recovery of vasospasm in contrast to continuation of histopathological changes on arterial wall may support this hypothesis. Further studies focusing on peripheral sympathetic discharge are needed. Our study points out benefits of dexmedetomidine in SAH. Although prevention of SAH is achieved in rabbits by clonidine, by another α_2 agonist, or by starting to establish it as SAH is forme, this is not the case in most clinical circumstances. Mostly, patients are admitted to physicians after they have experienced SAH in different neurological status. Our study shows that dexmedetomidine may be effective for alleviating vasospasm after the insult of SAH.

Conclusion

Although we have studied the effect of dexmedetomidine 48 h after experimental SAH, its effects after chronic vasospasm may also be studied. These studies may give us hope that dexmedetomidine may be used for its antivasospastic effects, as well. However, human studies should be done to prove antivasospastic effects of dexmedetomidine and its effects on the outcome of patients after SAH. As a result, the major finding of the present study indicates that dexmedetomidine may alleviate vasospasm 48 h after experimental SAH. However, detailed studies are necessary to examine these preliminary findings and to clarify the mechanisms of action.

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