

Local Effects of Papaverine on Normal, Atherosclerotic, and Vasospastic Carotid Arteries of Rabbits: An Experimental Study

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ABSTRACT

Objective: Papaverine is a direct-acting vasodilating agent that is frequently used in the treatment of vasospasm after subarachnoid hemorrhage. However, not much knowledge is available about the effect of papaverine on atherosclerotic vessels.

Material and Methods: Twenty-four New Zealand-type male rabbits were divided into 4 groups: normal, atherosclerotic, normal vasospastic, and atherosclerotic vasospastic vessels. The atherosclerotic groups (2 and 4) were fed with high cholesterol diet and the other groups with a normal diet for 4 weeks. Cholesterol levels were measured before and after exposure to these diets. In groups 3 and 4, a vasospasm model for common carotid arteries was established. In all subjects, papaverine was applied topically on the left common carotid artery (study subgroups a) and serum physiologic on the right (control subgroups b). Before and 10, 20, 30, 40, 50, and 60 minutes after topical application, vessel diameter was measured and compared between the groups. Histological evaluation of the artery was also performed in all subjects.

Results: In the atherosclerosis groups (Groups 2 and 4), blood cholesterol levels were significantly higher after 4 weeks of high cholesterol diet. Atherosclerosis and vasospasm development were confirmed with histological examination in the respective groups. Papaverine application lead to significant dilation in all groups according to the SF application. Its most prominent vasodilating effect was seen in normal vessels, while its effect gradually decreased from groups 2 to 4.

Conclusions: The vasodilating effect of papaverine decreased in the presence of atherosclerosis. New experimental and clinical studies are required to determine the effective local papaverine doses in atherosclerotic cases.

Keywords: atherosclerosis, papaverine, subarachnoid hemorrhage, vasospasm

ÖZET

Lokal papaverinin tavşan modelinde normal, aterosklerotik ve vazospastik damarlar üstündeki etkileri: Deneysel çalışma

Amaç: Papaverin doğrudan etkili bir damar genişletici ilaçtır ve subaraknoid kanama sonrası gelişen vazospazm tedavisinde sık olarak kullanılır. Ancak aterosklerotik damarlar üstündeki etkinliği çok iyi bilinmemektedir.

Gereç ve Yöntemler: Yirmi dört Yeni Zelanda tipi erkek tavşan 4 gruba ayrıldı: Normal, aterosklerotik, normal vazospastik ve aterosklerotik vazospastik damarlar. Aterosklerotik gruplar (2 ve 4) 4 hafta boyunca yüksek kolesterol diyetiyle, diğer gruplar normal diyetle beslendi. Kolesterol düzeyleri diyet öncesi ve sonrasında ölçüldü. Grup 3 ve 4'te ana karotis arterlere vazospazm modeli uygulandı. Bütün deneklerin sol anakarotis arterine lokal olarak papaverin (çalışma alt grupları a) ve sağ karotislerine serum fizyolojik (kontrol alt grupları b) uygulandı. Topikal uygulamadan önce ve 10, 20, 30, 40, 50 ve 60 dakika sonra damar çapları ölçüldü ve gruplar arasında karşılaştırıldı. Ayrıca bütün deneklerden alınan arter örnekleri histolojik olarak değerlendirildi.

Bulgular: Ateroskleroz gruplarında (2 ve 4) diyet sonrası kolesterol düzeyleri anlamlı olarak yükseldi. Ateroskleroz ve vazospazm gelişmesi uygun gruplarda histolojik olarak doğrulandı. Papaverin uygulanması tüm gruplarda serum fizyolojik uygulanmasına göre damarda anlamlı bir genişleme sağladı. En belirgin genişleme normal damarlarda görüldü, Grup 2-4'te genişletici etki giderek azaldı.

Sonuçlar: Papaverinin damar genişletici etkisi ateroskleroz varlığında azaldı. Aterosklerotik olgularda etkin lokal papaverinin dozunun belirlenmesi için yeni deneysel ve klinik çalışmalara ihtiyaç vardır.

Anahtar kelimeler: ateroskleroz, papaverin, susbaraknoid kanama, vazospazm

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Introduction

Cerebral vasospasm was described first by Gull in 1859 (1) and was angiographically shown by Ecker and Riemenschneider in 1951 (2). It is well known that the most frequent cause of mortality and morbidity is vasospasm in patients with spontaneous subarachnoid hemorrhage (SAH) presenting at the hospital (3). The etiopathogenesis of vasospasm after SAH is not exactly known (4,5). In vivo and in vitro studies showed that oxyhemoglobin appearing with the disintegration of red blood cells induces pathological processes developing into vasospasm. In addition, it is known that some neurogenic reflex mechanisms, other disintegration products of the blood, and potassium also play a role in pathogenesis (4,5). Presence of a correlation between immune complexes in the blood and severity of vasospasm is shown in newer studies, and it is thought that an autoimmune process may also play a role in the development of these reactions (6).

An exact and effective treatment modality for vasospasm has not yet been defined because we do not know its etiopathogenesis exactly. Some treatment modalities are being tried experimentally and clinically. One of them, papaverine, is an alkaloid found at 1% in opium extract (7). It is a very effective direct-acting vasodilator especially for arteries and arterioles (8). It was tried intrathecally, intra-arterially, and intravenously for experimental and clinical vasospasm treatment, and it was found to be very effective (4,9-11). However, its effects on atherosclerotic vessels are not known.

This study evaluated vasodilator effects of papaverine on atherosclerotic vessels with and without vasospasm in an experimental rabbit model.

Material and Methods

After approval by the local ethical committee, the study was performed at the Experimental Animal Research and Production Laboratory of Cerrahpasa Faculty of Medicine. Evaluation by light microscope was performed at the Clinical Pathology Laboratory of Okmeydani Training and Research Hospital.

Groups

In the study, 24 New Zealand-type male rabbits with a weight of 2.5-3 kg were used. They were randomly divided into 4 groups consisting of 6 rabbits each. Papaverine was topically applied on the left common carotid artery (CCA) of each

subject (as "a" subgroups) and serum physiologic (SF) was given to the right CCA (as "b" subgroups). Thus, the groups were as follows:

- Group 1a: Normal vessel with topical papaverine (0.3%) application (n=6)
- Group 1b: Normal vessel with topical SF application (n=6)
- Group 2a: Atherosclerotic vessel with topical papaverine (0.3%) application (n=6)
- Group 2b: Atherosclerotic vessel with topical SF application (n=6)
- Group 3a: Normal vasospastic vessel with topical papaverine (0.3%) application (n=6)
- Group 3b: Normal vasospastic vessel with topical SF application (n=6)
- Group 4a: Atherosclerotic vasospastic vessel with topical papaverine (0.3%) application (n=6)
- Group 4b: Atherosclerotic vasospastic vessel with topical SF application (n=6)

To Form Atherosclerosis

A rabbit model found in the literature was used to induce atherosclerosis (12,13). The subjects of Groups 1 and 3 were fed with normal diet and the subjects of Groups 2 and 4 were fed with a diet containing 2% cholesterol during 4 weeks. Cholesterol levels were measured in venous blood of all subjects before and after diet.

To Induce Vasospasm

A model found in the literature was used to induce vasospasm in CCA (14). The subjects of Groups 3 and 4 were anaesthetized with intramuscular 50 mg/kg ketamine and administration of 50 mg/kg xylazine. The subjects were kept in supine position on the table; a midline incision was performed after their anterior neck region had been shaved, and was cleaned routinely. Both CCAs were found with blunt dissection and were wrapped with small pieces of silastic sheaths. One cc arterial blood taken from the auricle artery was injected into the silastic wrapping on both sides. The layers were closed and the subjects were kept under routine cage conditions for 72 hours to await the development of vasospasm.

Measurements of Vessels

All subjects were anaesthetized with intramuscular 50 mg/kg ketamine and administration of 50 mg/kg xylazine. They were

kept in supine position on the table; a midline incision was performed after their anterior neck region had been shaved, and was cleaned routinely. Both CCAs were found with blunt dissection and their diameters were measured with a 0.1 mm scale ruler under an operating microscope at 0 minutes. The measurements were performed after opening the silastic wrapping in the subjects of Groups 3; 4. 2 ml papaverine solution (0.3%) was administered to the left CCA, and 2 ml SF was administered to the right CCA. Measurements were repeated 10, 20, 30, 40, 50, and 60 minutes after papaverine or SF applications. All measurements were also photographed (Pentax K-100, 28-80 Macro- and 200M objectives with 5 extension tubes).

Pathological Evaluations

All subjects were killed by application of high-dose anesthetics intravenously, and a sample of 1 cm length of each CCA was removed and fixed in a 10% formaldehyde solution. They were dehydrated with alcohol and were bathed in paraffin. Paraffin blocks were cut at a thickness of 5 microns after freezing. After deparaffinization in xylene (3 times), they were bathed in water and stained with hematoxylin eosin dye. All slides were evaluated under a light microscope (Olympus BX7, Japan) with x100 magnification and were photographed.

Statistical Evaluation

Graphpad Instat 3.0 software was used for statistical analyses. Nonparametric tests were preferred because of the small subject numbers in each group. To compare the papaverine and SF groups, Mann-Whitney U test was used, and to compare various parameters of all groups together, Kruskal-Wallis One Way ANOVA was used. Post-hoc evaluation was performed with Dunn's test. Changes in one group over time were compared using Wilcoxon test. $P < 0.05$ was accepted as statistically significant for all evaluations.

Results

Cholesterol levels of all groups at the beginning and 4 weeks after diet are shown in Table 1. In Groups 2 and 4, the cholesterol level was significantly increased after 4 weeks compared to their initial levels. However, there was no significant change in Groups 1 and 3.

Vessel diameters of all groups under initial conditions and after local papaverine/SF application are shown in Table 2 and changes are illustrated in Figure 1.

In Group 1, increases of vessel diameters in the first 30 minutes after papaverine application were statistically highly significant compared to the initial levels ($p=0.002$). Subsequently, it gradually decreased to the initial levels. In the

Table 1: Cholesterol levels in all groups before and after diet program.

Groups	Cholesterol level/before study (mean±SD; mg/dl)	Cholesterol level/4 w after study (mean±SD; mg/dl)	P
Group 1	59.30±22.72	68.80±42.33	0.788
Group 2	68.80±19.08	1873±401	0.002
Group 3	70.33±19.61	79.16±14.76	0.310
Group 4	61.17±15.59	1808±367	0.031

Statistically significant changes were shown as bold character.

Table 2: Changes of vessel diameters over time in all groups.

	0 m (mean±SD)	10 m (mean±SD)	20 m (mean±SD)	30 m (mean±SD)	40 m (mean±SD)	50 m (mean±SD)	60 (mean±SD)	% max increase (mean±SD)	% mean increase (mean±SD)
Group 1A	1.50±0.14	2.13±0.34	2.60±0.25	2.73±0.22	2.45±0.50	1.95±0.32	1.56±0.12	87.20±17.80	49.50±9.70
Group 1B	1.50±0.14	1.51±0.14	1.53±0.13	1.51±0.11	1.53±0.12	1.48±0.11	1.50±0.08	4.50±3.50	2.00±3.20
Group 2A	1.43±0.12	2.01±0.18	2.01±0.16	1.96±0.15	1.91±0.21	1.71±0.17	1.48±0.04	43.50±13.70	29.70±10.50
Group 2B	1.43±0.12	1.43±0.08	1.45±0.08	1.46±0.08	1.45±0.08	1.43±0.12	1.45±0.1	3.80±5.70	2.60±5.00
Group 3A	2.06±0.15	2.45±0.28	2.45±0.28	2.45±0.33	2.31±0.27	2.16±0.24	2.08±.21	21.80±4.60	12.30±3.10
Group 3B	2.05±0.18	2.05±0.13	2.08±0.16	2.08±0.17	2.08±0.17	2.06±0.18	2.10±0.20	3.90±1.90	1.40±2.60
Group 4A	2.08±0.36	2.38±0.41	2.41±0.42	2.25±0.39	1.96±0.40	2.13±0.34	2.11±0.34	18.60±4.50	7.80±3.60
Group 4B	1.63±0.34	1.65±0.25	1.71±0.23	1.66±0.29	1.70±0.32	1.63±0.29	1.68±0.27	8.20±9.60	2.00±4.40

m: minute

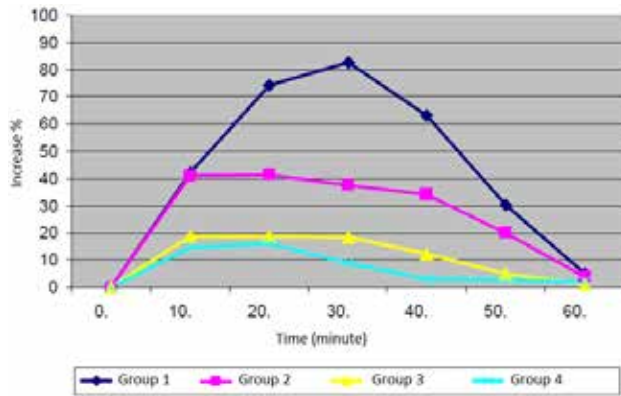


Figure 1: Vessel diameter changes over time in all groups.

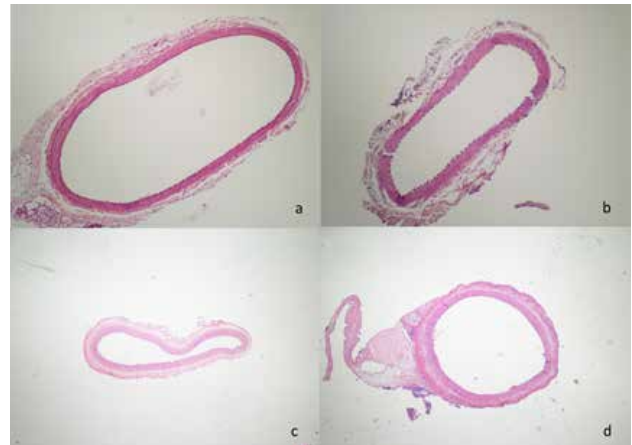


Figure 2: Histologic appearances of vessel sections in all groups. HE a) normal vessel, b) atherosclerotic vessel; c) normal vasospastic vessel; and d) atherosclerotic and vasospastic vessel.

Table 3: Comparison of maximal and mean changes in vessel diameters after papaverin and saline applications.

	p for max. increase	p for mean increase
Group 1	<0.001	<0.001
Group 2	<0.001	<0.001
Group 3	<0.001	<0.001
Group 4	0.03	0.03

other groups, changes in vessel diameters were generally not so prominent and decreased sooner with regard to the normal vessels. The increase in Group 4 was the lowest. In the b subgroups (SF application) of all groups, changes of vessel diameters were not significant over time in relation to the initial levels. In all groups, maximal and mean increases in vessel

diameters were statistically higher in the papaverine groups compared to those in the SF groups (Table 3).

For all groups, maximal and mean changes of vessel diameters after papaverine and SF applications are shown in Tables 4 and 5, respectively. Maximal increase of vessel diameter was significant in Group 1 compared to Groups 3 and 4 (Table 4), and mean increase of vessel diameter was significant in Group 1 compared to Groups 3 and 4, and in Group 2 compared to Group 4 (Table 5). There was no significant difference between vessel diameters between the Groups after SF application.

Table 4: Evaluation of all groups according to their rate of maximal increase in vessel diameter.

	Group 1	Group 2	Group 3	Group 4	p
Papaverine	87.2±17.8	43.5±13.8	21.8±4.6	18.6±4.5	0.0002 (post-hoc dunn: p<0.01 (1vs3) p<0.001 (1vs4) p>0.05
Saline	4.5±3.5	3.8±5.7	3.9±1.9	8.2±9.6	

Statistically significant values are shown bold

Table 5: Evaluation of all groups according to their rate of mean increase in vessel diameter.

	Group 1	Group 2	Group 3	Group 4	p
Papaverine	49.5±9.7	29.7±10.5	12.3±3.1	7.8±3.6	0.0002 (post-hoc dunn: p<0.05 (1vs3, 2vs4) p<0.001 (1vs4) p=0.98
Saline	11±4.4	1.5±6.3	1.4±2.6	2.0±4.4	

Statistically significant values are shown bold

Histological Findings

It was seen that the endothelial layer was thin and regular, the internal elastic lamina was thin and not undulated, and smooth muscle cells were located concentrically in the media layer in normal vessels; the thickness of the vessel walls was normal (Figure 2a). In Group 2, there was no typical atheromatous plaque; however, thickness, endothelial desquamation, subendothelial lipid deposition in the intima and media layers, elastic fibril degeneration in the media layer, and disarrangements of arrays of endothelial cells of CCAs of these rabbits were seen (Figure 2b).

In Group 3, there was a prominent decrease of vasospastic vessel inner diameter, a prominent increase of vessel wall thickness, breakdown of endothelial integrity in place, undulation of internal elastic lamina, and vacuolization in the media layer (Figure 2c). In Group 4, breakdown of endothelial integrity was more prominent than in Group 3. In addition, subendothelial lipid deposition, thicknesses of intimal and media layers, undulation of the internal elastic lamina, vacuolization of the muscular layer, and a prominent increase of thickness the of vessel wall were found (Figure 2d).

Discussion

Cerebral arterial vasospasm is a condition with cerebral arterial constriction due to SAH, brain injury, infection, or surgery. It is especially frequently seen after aneurysmal SAH. Mortality in patients with spontaneous SAH is about 45% in 1 month (15), and vasospasm is one of the major causes of this morbidity and mortality.

The pathophysiology of cerebral vasospasm is complex and multifactorial. Especially products of lipid peroxidation and oxyhemoglobin in hemorrhage regions are considered to be responsible. The degree and severity of vasospasm is related to the amount of cisternal blood (4,16). Various methods were tried to prevent development of vasospasm and to treat it once developed. Some procedures such as sedation, cardiopulmonary stabilization, or cerebrospinal fluid drainage procedures to reduce intracranial hypertension, hemodilution/hypertension/hypervolemia (triple H therapy) to increase cerebral perfusion, vasodilator agents such as papaverine and calcium canal blockers, and intraarterial procedures to widen the constricting arteries and arterioles are frequently used in clinical settings (17).

Papaverine is a vasodilator agent inhibiting cyclic nucleotide phosphodiesterase enzyme; thus it leads to an

increase of the levels of cAMP intracellularly. The last effect is a relaxation of vascular smooth muscles and vasodilation (4,18). There are various routes for the application of papaverine, of which the intraarterial and intracisternal use have been well studied (4).

Papaverine was first used in 1948 to prevent repeated cerebral ischemic events due to various conditions, and thereafter its role as a potent vasodilator agent for treatment of cerebral vasospasm was reported in *in vivo* and *in vitro* models (4,10,11,17,19). It is effective in treating cerebral vasospasm in humans by intravenous (20), intracisternal (18), and intraarterial routes (10,21,22). However, some clinical studies demonstrated that although intraarterial application decreased the vasospasm, it did not affect the outcome of the patients (22), which is probably due to its short-acting effects. In addition, it may lead to serious systemic complications. Intravenous application may cause cardiac arrhythmias (23). After intraarterial administration, midriasis, confusion, convulsions, serious hypotension, depression of the brain stem, bradycardia, and thrombocytopenia may be seen (18,23,24). Intracisternal application was tried to lessen the drug's systemic effects (5,18). Although not as frequent and severe as in intravenous or intraarterial applications, similar complications and side effects may be seen after intracisternal application, too (18).

Another limitation of the use of papaverine is that it is a short-acting drug because of its quick elimination by the liver. Therefore, topical application into the cisterna provides only a short-time activity. To get over this limitation, new studies are designed with controlled-release long-acting forms. These forms provide high local concentrations with low systemic toxicity for a long time (26,27), and it is thought that intracisternal application of controlled-release forms decreases the systemic side effects.

It is well known that more than half of the patients with aneurysmal SAH also suffer from atherosclerosis and hypertension. In clinical studies, different results related to vasospasm in the elderly were reported. It was stated that the frequency of angiographic vasospasm after SAH increased in the elderly in some cases, while in some cases it decreased and in others it remained almost unchanged (28-31). On the other hand, Lanzino et al. (28) reported that the incidence of symptomatic vasospasm increased with advancing age. It was also shown in other studies that the effects of vasoconstricting agents on cerebral arteries were more pronounced in patients of

an advanced age and those with atherosclerosis, hypertension, and hypercholesterolemia (32-35).

However, there is no study evaluating the effects of vasodilating agents such as papaverine on atherosclerotic vessels found in the literature. It has been reported that vasodilating responses induced by papaverine in intact vessels in the elderly are essentially unchanged in comparison with younger patients (36). In an experimental study evaluating the effects of aging on vasospasm after SAH in a rabbit model, Nakajima et al. (31) showed this to be controversial and reported that the duration of the efficacy of papaverine became significantly shorter with advanced age. However, the effects of the presence or absence of atherosclerosis were not evaluated directly in this study.

In our study, vasodilator effects of papaverine on atherosclerotic and vasospastic vessels were evaluated and compared with the responses of normal vessels. First, atherosclerosis was induced in two groups in a previously described model and its development was demonstrated histologically. The increase in vessel diameter in response to the vasodilator effect of papaverine in the normal vessel group was statistically higher than in the vasospastic and atherosclerotic vessel groups. It was equally higher in the atherosclerotic group compared to that in the atherosclerotic/vasospastic group. These results showed that the response of atherosclerotic

vessels to papaverine was weaker than the response of normal vessels, and the response of atherosclerotic/vasospastic vessels was also weaker than the response of normal vasospastic vessels. In other words, the presence of atherosclerosis decreased the vasodilator effect of papaverine, while adding vasospasm to atherosclerosis caused a greater decrease.

These results suggest that papaverine might not be effective for the treatment of vasospasm in routinely performed topical doses in the presence of atherosclerosis. Therefore, new experimental and clinical studies are required to determine the effective local papaverine doses in atherosclerotic cases.

Contribution Categories	Name of Author
Development of study idea	A.T., A.C.I., M.C.
Methodological design of the study	A.T., A.C.I., M.C., M.A.H., D.O.
Data acquisition and processing	A.T., M.C., M.A.H., D.O.
Data analysis and interpretation	A.T., A.C.I., M.C., M.A.H., D.O.
Literature review	A.T., M.C., M.A.H., D.O.
Manuscript write-up	A.T., M.C., M.A.H., D.O.
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