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Original Investigation

Proconvulsant Effect of Papaverine on Penicillin-Induced Epileptiform Activity in Rats

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ABSTRACT

AIM: Papaverine is a vasodilator agent that is an opium alkaloid. It exhibits its effects by inhibiting the phosphodiesterase enzyme. Papaverine administration is widely used to avoid symptomatic vasospasm after subarachnoid hemorrhage. We aimed, in this research, to study the effects of papaverine on the epileptic discharges stimulated by penicillin.

MATERIAL and METHODS: Adult female Wistar rats (220±30 g) were included in this research (n=30). Rats were anesthetized with urethane (1.25 g/kg) and then the left cerebral cortex was reached by opening a burr hole with a drill. Penicillin G sodium salt (500 IU)(200 IU/1 µl) was injected into the left lateral ventricle to produce epileptiform activity. Thirty minutes before penicillin G sodium injection, papaverine was administered at doses of 5, 10, 20 or 40 mg/kg intraperitoneally.

RESULTS: There was no significant difference in spike frequency between the control group and the groups given 5 mg/kg, 10 mg/kg or 40 mg/kg papaverine, while 20 mg/kg papaverine significantly increased the spike frequency ($p<0.05$).

CONCLUSION: Papaverine augments the epileptiform activity produced by penicillin injection. It is important to remember that papaverine might induce convulsions in patients who have epilepsy. More research is required to understand the mechanisms of the proconvulsant influence of papaverine in epilepsy.

KEYWORDS: Epilepsy, Female rat, Papaverine, Penicillin

INTRODUCTION

Vasospasm that develops following aneurysmal subarachnoid hemorrhage is a serious condition causing mortality and permanent damage. Angiographic vasospasm develops in about 70% of patients with aneurysmal subarachnoid hemorrhage. This reversible vasospasm generally occurs between the 3rd and 14th days (6,9,16). About 30% of these patients develop late ischemic deficit, symptomatic vasospasm, the causes of which include vasospasm, microvascular deficit and cortical spreading depression (18).

The exact cause of post-hemorrhagic constriction in cerebral arteries is not known. There are many factors known to cause vasospasm, such as structural changes in the cells of the arterial wall, erythrocyte breakdown products, serum lipids and some plasma proteins. These causes probably initiate a series of chain reactions leading to vasospasm (16).

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Systemic and endovascular treatment methods are used to treat cerebral vasospasm and include intra-arterial vasodilator substances like papaverine, nimodipine, nicardipine, milrinone, fasudil and verapamil (15).

Papaverine is a widely used opium alkaloid. The mechanism of vasodilator effect of papaverine is not exactly known. However, it is known that it increases intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels by inhibiting cAMP and cGMP phosphodiesterases in smooth muscle cells (11). Papaverine also blocks the calcium channels on the cell membrane and prevents the release of calcium from internal stores (10). Angiographic recovery was observed in 60-90% of the patients who received intra-arterial papaverine, while only 25-60% showed clinical recovery. It is also known that papaverine has a short-term effect because its half-life is about 2 hours (16). On the other hand, some studies report that papaverine increases intracranial pressure and vasospasm, causes damage in the gray matter and depression in the brainstem, induces epileptic seizures, and causes focal neurological deficits (1,7,15). Intra-arterial papaverine injection did not induce seizures in male Sprague-Dawley rats while it decreased the epileptiform activity induced by ketamine (8). Papaverine also showed a proconvulsant effect on theophylline-induced seizures in rats (17).

There are studies showing that papaverine has both convulsant and anticonvulsant effects. The aim of the current study was to elucidate the controversies about the effect of papaverine in epilepsy and to understand whether its use in brain surgery carries a risk of epilepsy by investigating the effects of papaverine in a penicillin-induced experimental epilepsy model.

MATERIAL and METHODS

This study included 30 adult female Wistar albino rats (220 ± 30 g). The rats were kept at the Animal Research Center of Ondokuz Mayis University in a 12 h light–dark cycle with *ad libitum* access to food and water. Procedures were carried out consistently with the local guidelines for the care and use of laboratory animals and the guidelines of the European Community Council for Experimental Animal Care. The experimental procedures were approved by the Animal Ethics Committee at Ondokuz Mayis University (12).

Following urethane (1.25 g/kg, i.p.) anesthesia of the rats, left cerebral cortices were exposed by removing the cranium by drilling a burr hole (12). The head of the rat was fixed in a stereotaxic device and then the recording electrodes were located on the cortex to record cortical electrical activity during electrocorticography (ECoG) (Figures 1A-E; 2A, B).

Penicillin G (500 IU/2.5 µl) was injected into the left lateral cerebral ventricle according to the Rat Brain Atlas of Paxinos (14). Papaverine was injected intraperitoneally at four different doses 30 minutes before the penicillin G injections.

Animals were divided into 5 groups each with 6 rats: The first group served as control and received only penicillin G injection. The second, third, forth and fifth groups received penicillin G and papaverine at doses of 15, 10, 20 and 40 mg/kg, respectively.

For statistical evaluation, one-way analysis of variance (ANOVA) was used, followed by Tukey's post hoc test to correct for multiple comparisons of groups. Data were stated as the mean ± the standard error of the mean (SEM). The significance level was $p<0.05$.

RESULTS

In the control group, epileptic spikes were induced 60 ± 11 s after intracerebroventricular injection of penicillin G (500 IU / 2.5µl). Epileptic activity became stable between the 20th and 30th minutes after injection. ECoG recording were obtained for 180 min (Figure 1A). Examples of ECoG recordings from rats injected with papaverine are presented in Figures 1B-E.

There was no significant difference in spike frequency between the control group and the groups given 5 mg/kg, 10 mg/kg or 40 mg/kg papaverine ($p>0.05$). However 20 mg/kg papaverine caused a significant increase in the spike frequency between the 90th and 170th minutes after penicillin G injection ($p<0.05$) (Figure 2B).

DISCUSSION

This study showed that the 20 mg/kg dose of papaverine significantly increased spike frequency of penicillin-induced epileptiform activity. Papaverine is one of the substances that are used topically or intraarterially to resolve the vasospasm that develops after subarachnoid hemorrhage due to an aneurysm (15). Papaverine administration may induce some side effects such as epileptic seizures. Epileptic seizures were reported in 33% of 876 patients who had intracerebral hemorrhage (7). The effect of papaverine on the induction of epileptic seizures is controversial. The reason for developing epilepsy following subarachnoid hemorrhage could be some blood products that diffuse into the brain tissue such as hemoglobin. It is already known that intracortical injection of hemoglobin induces epileptiform activity in rats (13).

Papaverine, an opium alkaloid, inhibits adenosine uptake and the phosphodiesterase enzyme and causes vasodilation in arteries via an unknown mechanism. Papaverine was also used in experimental epilepsy studies, some of which showed its proconvulsant effects while some others showed that it had anticonvulsant effects. Intraperitoneal injection of 35 mg/kg papaverine just before theophylline infusion showed a strong proconvulsant effects in Sprague Dawley rats (17). The mechanism of this proconvulsant effect was explained with papaverine being an adenosine receptor agonist. Although the rat strain and epilepsy model used are different, these results are in support of the current study. However it is known that adenosine showed anticonvulsant effects in various experimental epilepsy models. Focal and intracerebroventricular injection of adenosine in penicillin-induced experimental epilepsy significantly suppressed epileptiform activity, which contradicts the explanation of proconvulsant effect of papaverine via adenosine receptors

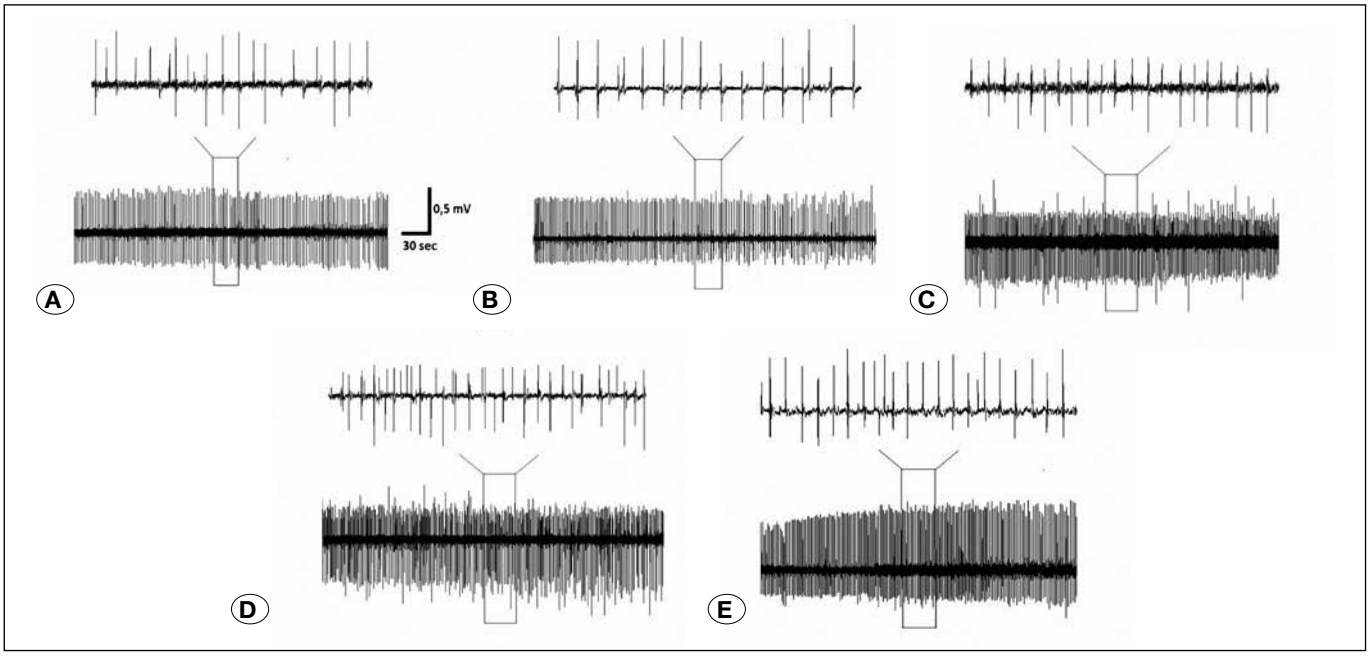

Figure 1: Examples of ECoG recordings from **A)** control, **B)** 5 mg/kg papaverine, **C)** 10 mg/kg papaverine**, D)** 20 mg/kg papaverine, and **E)** 40 mg/kg papaverine groups**.**

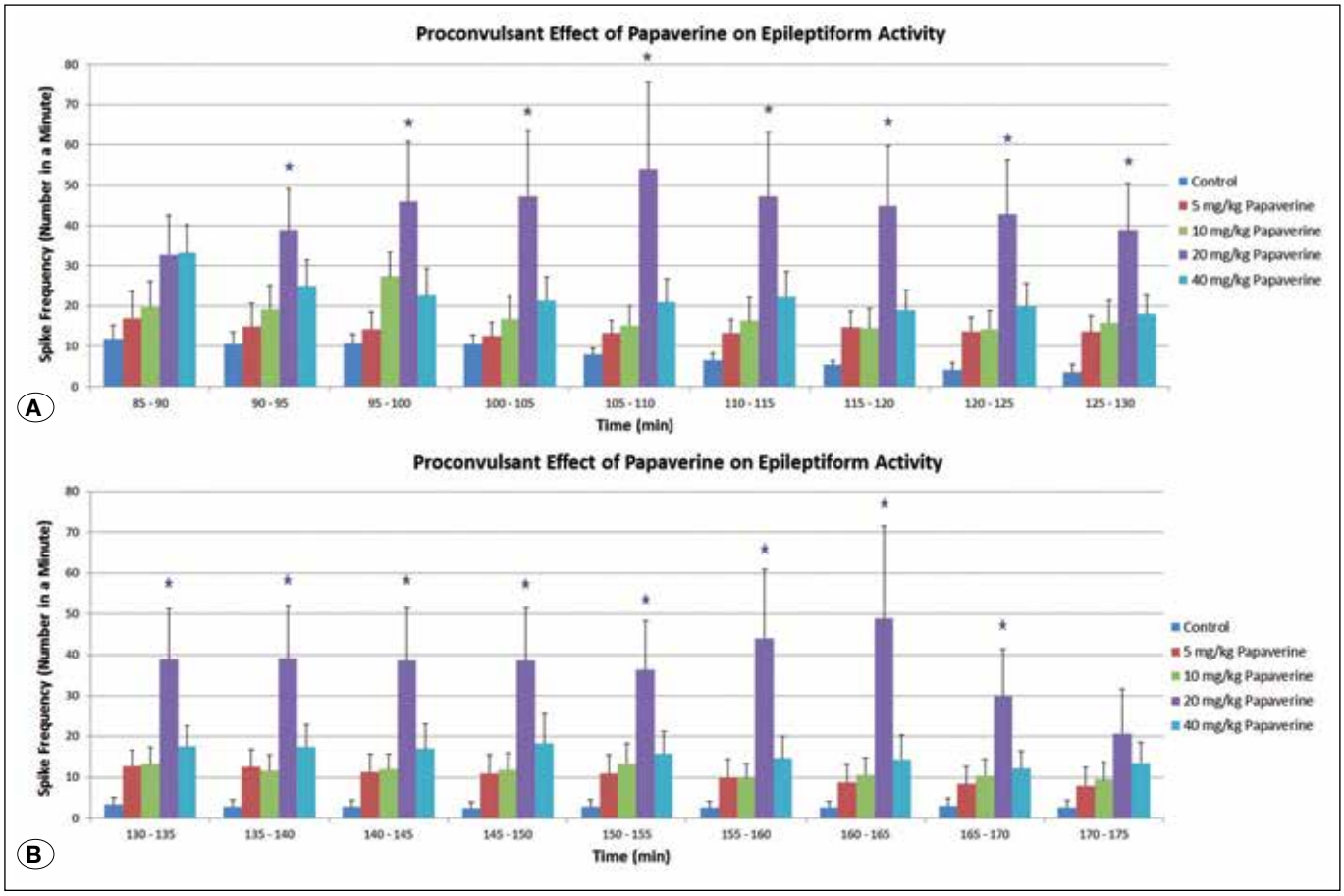

Figure 2: A) Five-minute averages of spike frequencies between 85th and 130th minutes, and **B)** five-minute averages of spike frequencies between 130th -175th minutes (mean ± SEM). *p<0.05.

(19). On the other hand, papaverine was shown to have anticonvulsant effects in the amygdala and hippocampal kindling epilepsy models (3,4). In hippocampal kindling model, maximum effect was observed 5 minutes after injection, while the effect disappeared after the 60th minute. Another study reported that intra-arterial injection of 14 mg/kg papaverine decreased the epileptiform activity induced by ketamine (8).

In the current study, experimental epilepsy was induced by injecting 500 IU penicillin G into the left lateral ventricle. Low dose penicillin blocks gamma-aminobutyric acid-A (GABA-A)-mediated inhibition by selectively antagonizing its receptors (2). Local injection of penicillin into the cortex initially induces focal epilepsy. Epileptiform activity that starts locally spreads all over the brain, which may induce clonic seizures (5). The results of the current study show that papaverine potentiates the epileptic discharges provoked by penicillin. Although the mechanism of this proconvulsant effect is not known, it is possible that papaverine may potentiate the penicillin effect by changing the membrane structure and membrane potential of the neurons. Further studies with other models of epilepsy may provide an explanation for the proconvulsant effect of papaverine.

Although the reason for the delayed effect of papaverine is not very clear, the intraperitoneal administration route of papaverine might be responsible. The proconvulsant effect of papaverine shown in the current study in the experimental penicillin epilepsy model may explain epilepsy development in some patients administered papaverine following subarachnoid hemorrhage.

CONCLUSION

Papaverine could be one of the factors that trigger seizures following subarachnoid hemorrhage in patients with an epilepsy history. The surgeons should consider its proconvulsant effect and administer antiepileptic drugs if necessary before using papaverine.

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