Clinical and experimental evaluation of the effect of Khat-induced myocardial infarction

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ABSTRACT

Objective: To evaluate the effect of Khat-induced myocardial infarction (MI) in Yemen.

Methods: One hundred and twenty patients with MI, admitted to Al-Thawra Hospital, Sana'a City, Yemen, during the year 2001 and 120 volunteer controls were collected for this study. On the other hand, we used 48 adult male rabbits for this study and divided it into 8 groups. Each group was consist of 6 animals; group I was used as normal control, group II was given adrenaline 60μg/kg intravenous infusion, group III and IV were given Khat 1g/kg once daily for 2 months, group V and VI were given Khat 1g/kg 3 times daily for 2 months, group VII and VIII were given Khat extract equivalent to 1g/kg intravenous infusion, 4 hours after the last dose of Khat and adrenaline 60μg/kg intravenous infusion was given to groups IV, VI and VIII. The animals were killed by decapitation. Blood samples were collected from each rabbit for determination of their creatinine kinase-iso enzyme (CK-MB) lactate dehydrogenase (LDH) and serum glutamic-oxaloacetic transaminase enzymes. Also, hearts were dissected out rapidly for histopathological study.

Results: Seventy-nine percent of patients with MI were Khat chewers and only 20.8% were non-Khat chewers. Experimental study shows that Khat in a dose of 1g/kg 3 times a day for 2 months, Khat extract equivalent to 1g/kg intravenous infusion alone and in combination with adrenaline 60μg/kg intravenous infusion significantly increased cardiac enzymes (CK-MB, aspartate transaminase, LDH), also, the histopathological study for the same groups revealed multiple areas of infarction.

Conclusion: The present study has demonstrated that Khat chewing may be considered as a risk factor for the occurrence of MI especially in persons who are susceptible to the disease. It is therefore, recommended that Khat chewing should be avoided in persons who have any cardiovascular problems.

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Khat had wide variety of effects on various body systems. Mancioli and Parrinello[1] detected cases of angina or disorders of the peripheral circulation, with increasing Khat use. Rymond-Hamet[2] showed that, Khat leave extracts increase adrenaline induced hypertension and renal vasoconstriction. Myocardial infarction (MI) is the necrosis of myocardial tissue as a result of prolonged ischemia. The rapidity and extent of the infarction are determined by the extent of reduction of blood flow to the area.[3] Traditionally, the pathogenesis of ischemic heart disease has been attributed to an imbalance of myocardial oxygen supply and demand.[4] Nabil et al[5] showed that, cathinone produced positive inotropic effect and chronotropic effect on isolated guinea pig heart. In central nervous system, Khatamines induce dopamine release in dopaminergic and serotinon (5-HT) release in a dose-

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dependent manner.[6] In peripheral nerves, Khatamines induce release of Nor-epinephrine from its storage sites lead to facilitate noradrenergic transmission lead to sympathomimetic effects.[7] Khat might be contribute to the migraine, hypertension, cerebral hemorrhage myocardial insufficiency and pulmonary edema.[8] The aim of this study is to evaluate the clinical and experimental effect of Khat-induced MI in Yemen.

Methods. One hundred twenty cases of patients with MI and 120 cases of normal healthy volunteers were collected for this study. On the other hand, we used 48 adult male rabbits for this study and divided it into 8 groups. Each group consist of 6 animals; group I was used as normal control, group II was given adrenaline 60μg/kg intravenous infusion, group III and IV was given Khat (fresh leaves) 1g/kg once daily for 2 months, group V and VI was given Khat (fresh leaves)1g/ kg 3 times daily for 2 months, group VII and VIII was given Khat extract equivalent to 1g (fresh leaves)/kg intravenous infusion, 4 hours after the last dose of Khat and adrenaline 60μg/kg intravenous infusion was given to IV, VI and VIII groups. After the last dose of Khat and 24 hours of adrenaline administration, the animals were killed by decapitation. Blood samples were collected from each rabbit for determination of their creatinine kinase-iso enzyme (CK-MB), lactate dehydrogenase (LDH) and serum gulutamic oxalacetic transaminase (SGOT) enzymes. Also, hearts were dissected out rapidly and put in 10% neutral buffered formalin for histopathological study. The animals in group II were given adrenaline 60μg/ kg intravenous infusion for induction of MI according to Chagoya, et al[9] method. After 24 hours, the animals were killed by decapitation. Blood samples were collected from each rabbit for determination of their CK-MB, LDH, and SGOT enzymes. Also, hearts were dissected out rapidly and put in 10% neutral buffered formalin for histopathological study. An antibody is incorporated in creatine kinase reagent for determination of serum creatine kinase (CK-MB). This antibody, will bind to and inhibit the activity of the M sub-unit of CK-MB. This means that only the activity of the B sub-unit in serum is measured. If the activity is multiplied by a factor of 2, it will give the activity of CK-MB in serum according to Stein, et al10 method. Using wavelength 340 nm, temperature 37^{0}C, then 0.1ml serum was mixed with 2.5ml reagent (adenosine diphosphate, adenosine monophosphate, diadenosine pentaphosphate, nicotinamide adenine dinucleotide phosphate [NADP] glucose-6-phosphate dehydrogenase [G_6PDH], N-acetylcysteine, creatine phosphate, and antibody of CK-MB) and stand at the appropriate temperature for 10 minutes. Then add a cuvette, and read absorbance A1. Then read absorbance A2 exactly 5 minutes later. Serum LDH and SGOT were measured according to Henry[11] method. For histopathological study, the sample was treated and examined according to Swarup et al[12] method. Fresh Khat leaves were homogenized or macerated with alcohol to be extracted according to Trease and Evans[13] method.

Results. ***Results of clinical study.*** One hundred twenty patients with MI, 73.3% were males and 26.7% females, mean age ± standard deviation was 53.3±11.8 years. One hundred and twenty normal healthy volunteers, 81.7% were males and 18.3% females, mean age ± standard deviation was 51±11.7 years. The results show that from 120 cases who had MI, there are 95 khat chewers a percentage of 79.2% while only 66 volunteers were khat chewers a percentage of 55% ($P<0.0001$). Also, it's shown that khat chewing among MI cases is 3.1 times more than that among controls (odds ratio = 3.1). In addition, it's shown that the occurrence of attack after chewing is more than that before chewing and this is more than that during chewing. The results of clinical study are presented in **Tables 1, 2 & 3**.

Results of experimental study. 1) Effect of adrenaline induced MI - Adrenaline in a dose of 60μg/kg induced a significant increased in serum level of creatinine kinase (CK), LDH and SGOT as compared with normal control. Also, the histopathological study of cardiac tissues of this group revealed multiple areas of infarction. 2) Effect of Khat leaves and extract alone and in combination with adrenaline on serum level of cardiac enzymes. The chronic oral administration of Khat leaves in doses of 1g/kg daily for 2 months induced a non significant increased in serum level of CK, LDH and SGOT enzymes, while in combination with adrenaline 60μg/kg intravenous infusion significantly increased as compared with normal control. Also, Khat leaves in doses of 1g/kg 3 times daily for 2 months and acute intravenous administration of Khat extract equivalent to 1g/kg (fresh leaves) alone and in combination with adrenaline 60μg/kg intravenous infusion significantly increased the serum level of CK, LDH and SGOT enzymes as compared with normal control. The results are presented in **Table 4**. 3) Histopathological study - Khat in a dose of 1g/kg 3 times a day for 2 months, Khat extract equivalent to 1g/kg intravenous infusion alone and in combination with adrenaline 60μg/kg intravenous infusion revealed multiple areas of infarction in the cardiac tissues of these groups.

Discussion. Khat leaves (*Catha edulis*) contains many pharmacologically active constituents (alkaloids). The most important one is cathinone. Cathinone produced an increase in blood pressure and heart rate. These changes where concomitant with the presence of cathinone in plasma.[14] Nencini et al[15] showed that Khat chewing induce significant increase in blood pressure (BP) and catecholamines in Khat native subjects. The effects of Khat was

Table 1

Age class (years)	Patients with MI n (%)	Normal healthy volunteers n (%)
20-30	5 (4.2)	5 (4.2)
31-40	14 (11.7)	23 (19.2)
41-50	32 (26.6)	30 (25)
51-60	37 (30.8)	35 (29.2)
61-70	28 (23.3)	26 (21.7)
71-80	4 (3.3)	1 (0.8)

n - number, MI - myocardial infarction

Table 2

Cases and controls	Khat chewers n (%)	Non-Khat chewers n (%)
Patients with MI	95 (79.2)	25 (20.8)
Normal healthy volunteers	66 (55)	54 (45)

x^2 = 15.87%, P<0.0001, n - number, MI - myocardial infarction

Table 3

Time of attack	n (%)
Before	26 (29.9)
During	18 (20.7)
After	43 (49.4)

no response from 8 patients
n - number, MI - myocardial infarction

Table 1 - Age group distribution of cases and controls.

Table 2 - Percentage of Khat chewers and non-Khat chewer patients with MI in comparison with normal healthy volunteers.

Table 3 - Time of attack of MI in Khat chewer patients.

Table 4 - Effect of chronic oral Khat leaves in doses 1g/kg daily, 1g/kg 3 times a day for 2 months and acute I.V. administration of Khat extract of 1g/kg alone and in combination with adrenaline 60 µg/kg on cardiac enzymes of rabbits (mean ± SD, n=6).

Treatment	CK (U/L)	LDH (U/L)	SGOT (U/L)
Normal control	19.65 ± 3.32	189.00 ± 27.37	34.33 ± 6.77
Adrenaline (60µg/kg)	234.33 ± 32.20*	276.83 ± 37.26*	63.83 ± 10.42*
Chronic oral administration			
Khat 1g/kg once daily	23.83 ± 5.88	238.33 ± 37.10	41.00 ± 8.77
Khat 1g/kg once daily + adrenaline 60µg/kg	251.67 ± 36.01*	638.17 ± 40.75*	66.33 ± 10.44*
Khat 1g/kg 3 times a day	31.67 ± 5.09*	265.00 ± 28.81*	46.83 ± 12.27*
Khat 1g/kg 3 times a day + adrenaline 60µg/kg	777.67 ± 54.93*	316.33 ± 27.29*	65.83 ± 7.41*
Acute I.V. administration			
Khat extract 1g/kg I.V.	322.67 ± 25.98*	440.67 ± 41.79*	52.17 ± 9.41*
Khat extract 1g/kg I.V. + adrenaline 60µg/kg	225.67 ± 27.54*	510.83 ± 79.15*	74.17 ± 9.41*

* Significant difference as compared with normal control at p<0.05,
CK - creatine kinase, LDH - lactic dehydrogenase, SGOT - serum glutamic-oxaloacetic transaminase,
SD - standard deviation, n - number, I.V. - intravenous

attributed to induction of catecholamine release. It was found that (L)-cathinone induced release of catecholamine form rabbit heart tissue - prelabelled with H^3- noradrenaline. The peripheral noradrenaline sites (rabbit heart) were observed to be more sensitive than central nervous system dopamine site.[6,7,16] Yanagita[17] suggested that cathinone act by facilitating noradrenergic transmission and responsible for the sympathomimetic syndrome observed after Khat consumption and increase in inotropic effect. In the clinical study of this work, it was found that 79.2% of patients who had MI are Khat chewers. Also, the occurrence of attack after chewing Khat is more than before chewing and this is more than that during chewing. There is a significant increase in the total count of platelets in Khat fed rabbits and this is considered as one of the precipitating (risk) factors, for MI attack.[18] Abnormalities of coronary vascular tone and platelet aggregation or thrombus formation also contribute to ischemic heart disease development.[4] In this study, intravenous infusion of adrenaline in a dose of 60µg/kg induced a significant increased serum level of CK, LDH and SGOT of rabbits. Also, the histopathological study of cardiac tissues of this group revealed multiple areas of infarction. On the other hand, the chronic oral administration of Khat leaves in doses of 1g/kg daily for 2 months induced non-significant increased in serum level of CK, LDH and SGOT enzymes, while in combination with adrenaline 60µg/kg intravenous infusion significantly increased. Also, Khat leaves in doses of 1g/kg 3 times daily for 2 months alone and in combination with adrenaline 60µg/kg intravenous infusion significantly increased the serum level of CK, LDH and SGOT enzymes. The major determinants of myocardial oxygen consumption include heart rate, contractility, and systolic wall force. Alterations in the major determinants of myocardial oxygen demand, including increase in heart rate, contractile state and myocardial wall tension may increase infarction size.[19] In the present study, acute IV administration of Khat extract in a dose equivalent to 1g (fresh leaves)/kg induced a significant increased in serum level of CK, LDH and SGOT enzyme alone and in combination with adrenaline 60µg/kg intravenous infusion of experimental animals. Acute administration of Khat extract resulted in dose dependent chronotropic effect, and an increase in the amplitude of ventricular action.[16] Myocardial damage appears to be directly correlated with the amount of CK-MB released into the serum namely the higher the amount of CK-MB, the more extensive the MI.[20] Serum gulutamic oxalacetic transaminase is found in very large concentrations in heart and liver tissues, but only in moderate amounts in skeletal muscle, kidney and pancreas. The enzyme LDH is present in high concentration in heart, kidney, liver, and skeletal muscle.[19]

In this study, it was found that the microscopic examination of sections of the cardiac tissues of all groups revealed multiple areas of infarction except with those administered Khat leaves 1g/kg daily orally. Mancioli and Parrinello[1] detected cases of angina or disorders of the peripheral circulation, with increasing Khat use. The effect of Khat-induced MI is may be due to induction of catecholamines release and increased total count of platelets. The present study has demonstrated that Khat chewing may be considered as a risk factor for the occurrence of MI attack especially in persons who are susceptible to the disease. It is therefore recommended that Khat chewing should be avoided in persons who have any cardiovascular problems.

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