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Research Article

Khat Chewing Effect on the International Normalized Ratio in Patients with Mechanical Heart Valves under Warfarin Therapy

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Abstract

Background and Objective: Khat is a plant that contains the alkaloids cathine and cathinone which have some amphetamine-like properties. It is cultivated and its leaves chewed for their euphoric effect. This study intended to elucidate the effect of khat chewing on blood coagulation by using the International Normalized Ratio (INR) value as a calculable benchmark. **Materials and Methods:** In this cohort study, 146 patients with Mechanical Heart Valves (MHV) were assessed for two consecutive visits at one-month intervals. For each visit, the date of surgery, the patient's compliance, the dose of warfarin and the INR reading were assessed by the researcher. **Results:** Out of 146 patients with MHV, the mean age was 33.72 ± 12.43 years (range, 14-65 years); 82 (56.2%) were female and 64 (43.8%) were male. The results revealed that the mean of absolute INR readings was lower in khat-chewers than non-chewers by average 0.2 on the first and second visits ($p = 0.038$ and 0.002 , respectively). **Conclusion:** Khat chewing has a significant coagulant effect. There was a significant decrease in the value of INR for khat chewers patients with MHV when compared to non-khat chewers.

Key words: Khat-chewing, coagulation effect, mechanical heart valves, myocardial infarction, warfarin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Khat (*Catha edulis*) is a plant that contains the alkaloids cathine and cathinone which have some amphetamine-like properties. It is cultivated and its leaves chewed for their euphoric effect¹. Frequent khat chewing in the long-term has been associated with various health problems including esophagitis, gastritis, duodenal ulcer, liver cirrhosis, pulmonary edema and Myocardial Infarction (MI)². Several studies reported that khat chewing is associated with Ischemic Heart Disease (IHD) and acute cerebral stroke due to the effect of increased Blood Pressure (BP) in khat chewers^{2,3}.

Khat leaves are habitually chewed for several hours because of their psycho-stimulant effect, which is similar to amphetamine-like effect and can be considered as a risk factor for dental caries^{4,5}.

However, khat chewing is a common social habit in East Africa, parts of the Arabian Peninsula including Yemen and in the Indian Ocean countries like Madagascar and it has been neglected in scientific researches by public health scientists for decades⁵. Khat chewing is a very widespread social habit in Yemeni people including women and teenagers and it results in unfavorable outcomes^{5,6}.

Prothrombin Time (PT) and the international normalized ratio (INR) are laboratory measurements routinely used to assess the risk of bleeding or thrombosis. INR is a standard for reporting the effect of oral anticoagulant drugs on blood clotting⁷. Lifelong oral anticoagulation therapy such as Warfarin is recommended in patients undergoing Mechanical Heart Valves (MHV) replacement, to prevent thromboembolic events. The optimal INR values for MHV patients are within the range of 2 to 3.4. Current American and European guidelines recommend higher INR for anticoagulant therapy in mechanical mitral valve replacement than in aortic valve replacement⁸. Warfarin is the most common anticoagulant drug used in patients with MHV⁹.

As mentioned, khat chewing is a widespread social habit in many regions that has been neglected in scientific researches and due to lack of previous studies covering this topic, this study was introduced to elucidate the effect of khat chewing on blood coagulation by using the INR value as a calculable benchmark. To the best of our knowledge, this is the first study in the world to cover this significant topic.

MATERIALS AND METHODS

Ethics: Institutional ethical approval was received for this study. Informed consent was obtained from each patient

enrolled in this study. Confidentiality of the patient's information was assured during and after the study.

Patients selection: This prospective cohort study was conducted at Al-Thawra Modern General Hospital (TMGH) in Sana'a, the Republic of Yemen in the period from January to December 2019. In this study, 146 patients with MHV were assessed for two consecutive visits at one-month intervals at the cardiology outpatient clinic (OPD).

Study design: Firstly, consents were obtained and then, a structural interview was performed with the patients enrolled in this study, individually. Finally, an appointment for the next visit was arranged to be one month later. This study includes two consecutive visits at one-month intervals (INR-1 and INR-2). This was done to follow up on the study parameters. Accurate warfarin doses were prescribed for the patients, regarding their ages and health cases, by a qualified cardiologist. The warfarin doses were ranged from 1 to 10 mg (mean = 4.45 ± 1.65 mg). The target was to preserve INR value within the 2-4 range.

During each visit, the date of surgery, the patient's compliance, the warfarin dose, INR reading, khat-chewing and any hemorrhagic events were recorded by the researcher. Exclusion criteria include; 1) patients who could not record all INR readings and 2) patients who lost in second vision.

Statistical analysis: Data analysis was performed using the SPSS program. Data are presented as frequency and percentage for continuous variables and Mean \pm standard deviation (SD) for descriptive variables. Independent-samples T-test was done to show the difference in means between the two visits. A chi square test was used to evaluate the significance of the results. P-value was assumed to be significant when <0.05 .

RESULTS

In total 146 patients with MHV who underwent follow up for two consecutive visits in a one-month interval at the cardiology OPD were included in this study. The mean age was 33.72 ± 12.43 years (range, 14-65 years); 82 (56.2%) were female and 64 (43.8%) were male (Table 1).

Figure 1 shows the khat tree and khat herbs ready for chewing. Mitral valve alone was the replaced valve in 64 (43.83%) patient, aortic valve alone was the replaced valve in 22 (15.1%) patient and both mitral and aortic valves were in 60 (41.1%) patient (Fig. 2).



Fig. 1: Images of (a) Khat tree and (b) Khat herbs ready for chewing

Table 1: Sociodemographic characteristics of the patients involved in this study

Age	Male No. (%)	Female No. (%)	Total No. (%)
<20 years	14 (9.6)	18 (12.3)	32 (21.9)
20-29 years	10 (6.8)	6 (11)	26 (17.18)
30-39 years	16 (11)	21 (14.4)	37 (25.3)
40-49 years	16 (11)	13 (8.9)	29 (19.9)
50-59 years	7 (4.8)	12 (8.2)	19 (13)
≥60	1 (0.7)	2 (1.4)	3 (2.1)
Total	64 (43.8)	82 (56.2)	146 (100)

Table 2: Distribution of the patients according to INR readings on the two visits

No. of visit	INR result			Total No. (%)
	≤2 No. (%)	2.1-4 No. (%)	>4 No. (%)	
INR-1	23 (15.8)	114 (78.1)	9 (6.2)	146 (100)
INR-2	6 (4.2)	132 (91.7)	6 (4.2)	144 (100)

INR: International normalized ratio, INR-1: INR on the 1st visit, INR-2: INR on the 2nd visit

Table 3: Difference in INR readings in khat-chewers and non-khat chewers

	Khat-chewing	No. of patients	Mean	SD	p-value
INR-1	Yes	49	2.698	0.6479	0.038
	No	97	2.860	0.9562	
INR-2	Yes	47	2.585	0.4644	0.002
	No	97	2.837	0.8237	

Independent-samples t-test shows significant difference in INR values between khat-chewers and non-khat chewers both in the 1st and the 2nd visits

The enrolled patients were divided into khat-chewers 47 (32.19%) patients and non-chewers 97 (66.33%) patients. Khat

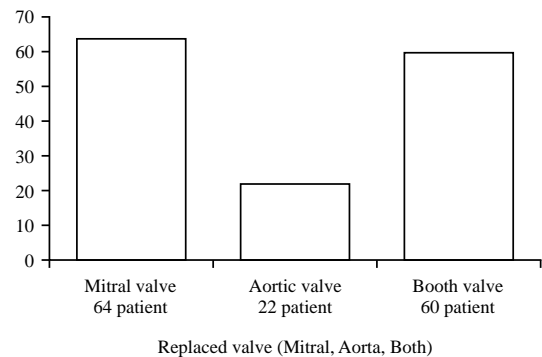


Fig. 2: Study of distribution of the replaced valves in the enrolled patients

chewers were subdivided into regular chewers who chew khat everyday 19 (40.42%) and irregular chewers who chew khat sometimes 30 (63.83%) (Fig. 3).

Table 2 shows the distribution of the patients according to the INR readings during the two visits, furthermore, it shows two unrecorded INR readings of two lost patients during the second visit.

The results revealed that absolute INR readings were lower for khat-chewers than non-khat chewers, by an average of 0.162 on the first visit and 0.252 on the second visit ($p = 0.038$ and 0.002 , respectively) (Table 3).

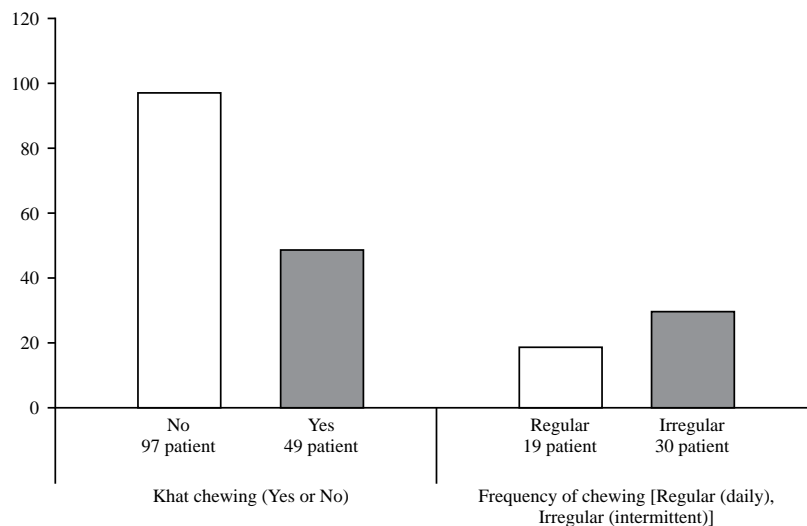


Fig. 3: Study of the gender distribution of the patients, the khat chewing habit (yes or no) and the frequency of khat chewing, either regular (daily) or irregular (intermittent)

DISCUSSION

Khat chewing is a widespread social habit in many regions that have been neglected in scientific researches. Here, this study was introduced to elucidate the effect of khat chewing on blood coagulation using the INR value as a calculable benchmark. In this cohort study, assessment of the INR of the patients with MHV was done on two consecutive visits at one-month intervals (INR-1 and INR-2). The study found a significant decrease in INR value in khat chewers when compared to non-khat chewers that revealed a significant coagulant effect of khat. In a review of the available previous studies about the effects of khat chewing, Abebe¹⁰ reported that khat can offset the cardio-protective effect of aspirin and to counteract the effect of antihypertensive, antiarrhythmic and also local anesthetic drugs. This effect is consistent with the results of the current study. Mega *et al.*¹¹ and El-Menyar *et al.*¹² reported that both diastolic and systolic BP and also heart rate was higher in khat chewers than non-khat chewers. In addition, khat chewing has either a causative or worsening effect on MI that was explained by the vasomotor effect of khat on the coronary arteries¹¹⁻¹³. Mega *et al.*¹¹ and Ali *et al.*¹⁴ reported that khat chewing increase the risk of recurrent MI, ventricular arrhythmia, cardiogenic shock and stroke. Sallam *et al.*¹⁵ reported that khat ingestion contributes to increasing both systolic and diastolic blood pressure but has no effect on HR. Admassie and Engidawork,¹⁶ reported that chronic use of a high dose of khat has a significant risk for cardiovascular problems. Al-Motarreb *et al.*¹⁷ reported that Acute Myocardial Infarction

(AMI) is associated with khat-chewing with a 39-fold increase risk of AMI in heavy khat-chewers. The previous studies reported significant effects of khat chewing on the cardiovascular system that increase the risk of cardiovascular problems especially the risk of myocardial infarction. The results of the current study supported the results of these studies and reports a coagulation effect of khat chewing.

Unfortunately, there is no previous studies about the coagulation effect of khat chewing to compare with the results of this study. This is the first study to cover this topic and here is its novelty. It is a good addition to the available information about khat chewing. This study is limited in the limited sample size. The patients of MHV usually don't chew large doses of khat like healthy peoples and that had a probably significant effect on the results.

CONCLUSION

Khat chewing has a significant coagulant effect. There was a significant decrease in the value of INR for khat chewers patients with MHV when compared to non-khat chewers in both visits. Thus, Patients with MHVs should avoid khat chewing.

SIGNIFICANCE STATEMENT

This study discovers the coagulant effect of khat chewing that can be an additional risk to the hazards of khat which is a widespread social habit in many countries, furthermore, it is a neglected problem in scientific researches. This paper is a

valuable new addition to knowledge about khat and it is useful for MHV patients and cardiologists.

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