Ulutas Med J 2018;4(2):78-84
DOI: 10.5455/umj.20180117091224

ORIGINAL ARTICLE OPEN ACCESS

Effect of Ramadan Fasting on the International Normalized Ratio in Patients with Mechanical Prosthetic Heart Valves

Mohammed Ghormalla Alghamdi [1] · **Abdullah Adel Kokandi** [2] · **Rheema Ahmad Alfadhil** [3]
Lama Abdullah Alotaibi [3]

[1] King Abdulaziz Cardiac Center, King Saud bin Abdulaziz University, Riyadh, Saudi Arabia
[2] Al Imam Mohammed ibn Saud Islamic University, Riyadh, Saudi Arabia
[3] King Saud University Medical City, King Khalid University Hospital, Riyadh, Saudi Arabia

Background: The effect of relegious Fasting and altered lifestyle pattern during the Holy month of Ramadan on the INR stability has not been previously studied in the Saudi population. We aimed to evaluate the effect of Ramadan fasting on the INR stability in patients using warfarin anticoagulation for mechanical prosthetic heart valves.

Method: Data were extracted retrospectively from a specialized anticoagulation clinic electronic database and were anlysed in a case-control manner, where Ramadan INR of each study subject was compared to his/her own pre-Ramadan INR level. Using Point-Of-Care (POC) testing, the first INR level during Ramadan was compared to the average baseline INR readings over the last 3 months before Ramadan. Study was conducted between July 29th and August 20th 2015, which corresponds to the month of Ramadan, 1436 Hejra Calendar.

Results: One-hundred and fourteen consecutive patients fulfilled the inclusion criteria. Mean age was 48.4±13.6 and males constituted 58% of cases. Low target (INR: 2-3) and high target (INR: 2.5-3.5) therapeutic ranges represented 35% and 65% respectively. Mean INR level was 2.81 at baseline and 2.75 during Ramadan with no statistically significant difference between them (P=NS). Achieving the desired target INR level before Ramadan was feasible in 62.5% and 64.8% of the low and high INR target groups, respectively. However, maintaining the desired INR level during Ramadan was feasible in 67.5% and 51.3% of the low and high target INR groups respectively (p=0.07). Duration of anticoagulation, warfarin and adherence scale did not contribute significantly to the primary outcome.

Conclusion: Ramadan fasting and its associated lifestyle changes in the Saudi community may aggravate the INR fluctuations in warfarin-treated patients. During Ramadan, warfarin-treated patients are more prone to develop supra-therapeutic INR and therefore they deserve careful attention and closer INR monitoring.

Keywords: Anticoagulation, INR, Ramadan, Fasting, Mechanical Heart Valves

Introduction

Around the world, a Muslim population of more than 1.6 billion perform an obligatory religous act of Fasting (Siyam) during the Holy month of Ramadan, which correspond to the 9th month of the Hijra Calendar (1). Religious fasting includes abstenance from food and drink from dawn to dusk (2). During Ramadan a lot of Muslim societies undergo significant lifestyle modifications, including dietary pattern. These dietary modifications, along with the prolonged day-time fasting and medication

Corresponding Author: Mohammed Ghormalla Alghamdi; Cardiology, King Abdulaziz Cardiac Center, King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia
E-mail: bmujahid@gmail.com
Received: Jan 16, 2018 **Accepted**: April 22, 2018
Published: June 29, 2018

scheduling changes may adversly effect the anticoagulation status of patients using Vitamin K Antagonsit (VKA) (3,4). Despite the recent advances in the field of oral anticoagulants, VKA remain the standard and most effective and reliable oral anticoagulants used in mechanical prosthetic heart valve pateints (4). Available studies on the effect of Fasting on the International Normalized Ratio (INR) were conducted in different geographic areas of the world, not including Saudi Arabia. These studies included diverse patient populations with widely variable cultural and social backgrounds and ended up by inconsistent results (5-8). Our study came to evaluate this unresolved issue in the Saudi community, using a larger sample size of a more homogeneous population. The aim of this study was to evaluate the potential effects of Fasting and lifestyle changes during Ramadan on the INR level in patients using VKA (Warfarin) for mechanical prosthetic heart valve anticoagulation at King Abdulaziz Cardiac Center (KACC) in Riyadh, Saudi Arabia. Out-come of this study is relevant to a large number of patients who are committed to a lif-long anticoagulation with VKA and very important for health care practicioners who are managing these individuals.

Methodology

Institutional Review Board (IRB) approval for conducting this study was obtained from King Abdullah International Medical Research Center (KAIMRC) under Protocol: RSS15/011. Study was conducted on patients who attended the Prosthetic Valve Anticoagulation Clinic (PV-ATC) at King AbdulAziz Cardiac Center (KACC), Riyadh, Saudi Arabia between 29 July and 20 August 2015, which corresponds to the month of Ramadan, 1436 Hejra Calendar. Male and females who were 15 years of age or older and have had a single or double mechanical prosthetic heart valves at any valve position were eligible for inclusion in the study. To be enrolled, patients signed an insormed consent and were required to have two or more INR readings taken at least one week apart over a period of 3-4 months preceding Ramadan, and at least one INR reading during Ramadan.

Patients with major baseline INR fluctuations (<1.5 or >4.5) were excluded as well as patients with any of the following conditions; chronic liver disease, severe tricuspid regurgitation, severe pulmonary hypertension, acute heart failure decompensation, and non-fasting patients. Recent antibiotic treatment, recent hospitalization for cardiac reasons or recent thromboembolic or hemorrhagic events, within three months prior to Ramadan, were additional reasons for exclusion. INR readings in the first four days of Ramadan were discarded, as a washout period, in order to allow for the effect of fasting and other lifstyle changes to take place. All INR measurments were done using the Point Of Care testing (POC), using the *CoaguChek® XS Plus System,* which has been validated against laboratort INR and proved to be reliabile (9). Demographic, clinical and laboratory data were collected from the electronic Prosthetic Valve Anticoagulation Clinic database and were entered into an electronic data collection form (MS Excel, 2013).

Data were analyzed in a case-control fashion, where each patient served as his/her own control. For each patient, the first INR reading during Ramadan was compared to his/her own average baseline INR reading before Ramadan. Absolute difference in the INR level between Ramadan and average pre-Ramadan readings was calculated as well as the effect of several clinical variables on the INR, using paired T-test.

Continuous variables were presented as mean ±standard deviation (SD), while categorics were expressed in number and percentage. P<0.05 at 95% confidence was consided as statistically significant. Statstical analysis was performed using IBM-SPSS Statistical software, version 23.

Results

Out of one hundred and ninety-five (195) patients who attended the PV-ATC during the study period, 114 patients were enrolled in the study and 81 patients were excluded due to various reasons (Figure-1).

Table 1. Baseline characteristics of the study population

Variable	Results
Age (Years)	48.5±13.6
Male gender	66 (57.9)
Mechanical Valve Position	
Aortic alone	53 (46.5)
Mitral alone	37 (32.5)
Aortic and Mitral	22 (19.3)
Tricuspid	2 (1.8)
First Ramadan on Warfarin	
Yes	24 (21)
No	90 (79)
Duration of Anticoagulant Use	
<6 months	22 (19.3)
6-12 months	8 (7)
>12 months	84 (73.7)
INR Therapeutic Range	
(2.0-3.0)	40 (35.1)
(2.5-3.5)	74 (64.9)
Warfarin Adherence Scale	
0	36 (40.5)
1-3	49 (55)
>=4	4 (4.5)
Weekly Warfarin Dose	34.16±1.4
Weekly Warfarin Dose	
<25	33 (29)
25-45	54 (47.4)
>45	27 (23.7)
Ejection Fraction (%)	51.6±7
Atrial Fibrillation	
Yes	39 (34.2)
No	75 (65.8)

Baseline characteristics of the population are shown in table-1. Mean age was 48.4±13.6 with 57.9% of them being males. Number of patients at high target INR (2.5-3.5) group was 74 (64.91%) and the remaining patients fell into the low target INR (2.0-3.0) group.

Table 2. Average International Normalized Ratio (INR) difference between baseline and Ramadan levels in relation to some risk predictors.

Variable	INR ΔMean	Mean 95% CL	P
Average INR difference	0.1	(0 – 0.3)	0.1
Duration of Anticoagulant Use			
<6 months	0.1	(-0.4 – 0.6)	0.5
6-12 months	-0.2	(-0.7 – 0.3)	0.3
>12 months	0.2	(0 – 0.4)	0.08
Target INR range			
2-3	0.2	(-0.1 – 0.5)	0.2
2.5 – 3.5	0.1	(-0.1 – 0.3)	0.2
Adherence Scale			
0	0.2	(-0.1 – 0.4)	0.1
1-3	0.1	(-0.2 – 0.3)	0.6
>=4	1.4	(-2.0 – 4.8)	0.2
Weekly Warfarin Dose			
<25	-0.1	(-0.4 – 0.3)	0.7
25-45	0.2	(-0.1 – 0.4)	0.1
>45	0.2	(0 – 0.4)	0.1

Mean baseline INR was 2.81 and mean INR during Ramadan was 2.75, with no statistically significant difference (95% CI: 0.03-0.3, p=0.1). Similarly, no significant difference was noted between Ramadan and baseline INR levels in any of the study subgroups based on; the duration of anticoagulation, warfarin dose, adherence scale and target therapeutic range (Table-2). Achieving the desired INR level in the low target INR range of 2.0-3.0 was feasible in 62.5% and 67.5% before and during Ramadan respectively (P= 0.3), while in the high target INR range (2.5-3.5) the desired levels were achieved in 64.86% & 51.35% before and during Ramadan respectively (p= 0.07).

Figure 1. Flow chart of the enrolment process of the study subjects

Figure 2. Bar chart graph showing the proportion of patients above, below and within the therapeutic range of International Normalized Ratio (INR)

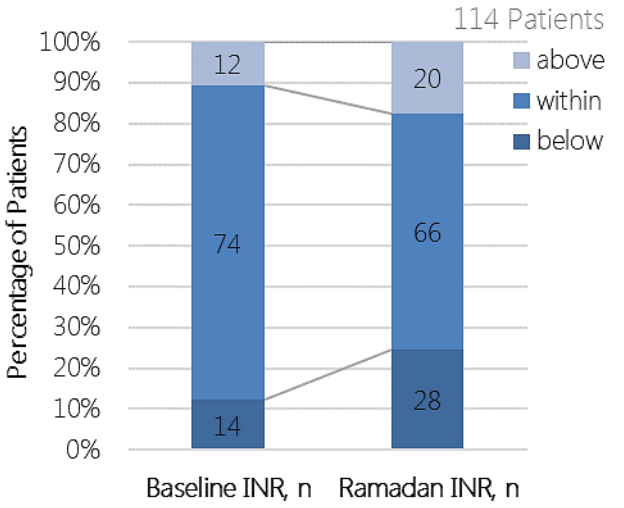
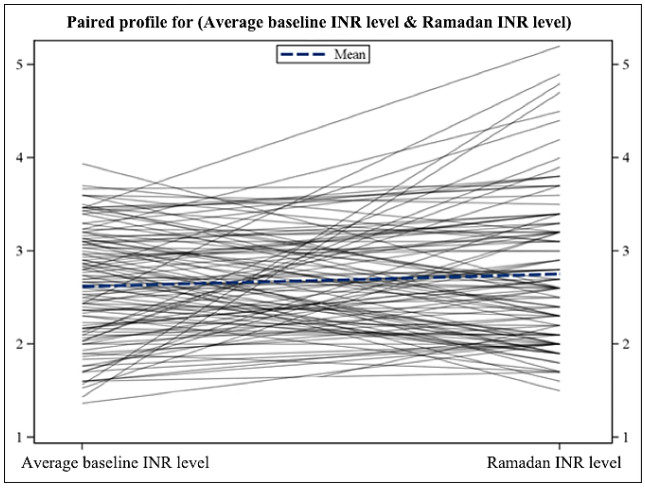


Figure 3. Trends of INR between baseline and Ramadan levels for the individual patients



Discussion

Patients with mechanical heart valves show a high risk population for developing thrombo-embolism, especially if accompanied by additional risk factors, like atrial fibrillation and impaired ventricular function. Warfarin remains the anticoagulant of choice for mechanical heart valve patients. Disadvantages of warfarin include its adverse interaction with several dietary items and pharmacological agents, a frequent problem that might lead to over or under anticoagulation. Degree of adherence to warfarin dosage and dose scheduling is another factor that might affect INR stability. Warfarin-diet interaction and loose medication adherence may both exist during Ramadan. Applying strict inclusion/exclusion criteria in study population would minimize the chance of having significant INR variations due to factors other than Ramadan, like conditions that predispose to liver dysfunction, anticoagulation interruption and drug-drug interactions (10,11).

The mean difference between baseline INR and Ramadan INR was <0.1, which is statistically insignificant. This finding is consistent with the result of a prior study on 70 patients with mechanical prosthetic heart valves, conducted in Egypt and showed no significant difference in the mean INR levels during and after Ramadan (8). A similar result was also concluded from a recently conducted prospective study from Turkey, where INR level was checked on a weekly basis for 3 months including Ramadan (7). In contrary to our findings, there are two other studies which have reported a significant increase in the mean INR during Ramadan (5, 7). The first one was conducted in the far east on a small sample size (32 patients) using warfarin, mostly for non-valve-related indications (6), and the other one was conducted in North Africa and included 67 patients who were treated with another form of KVA (Acenocumarol)(5). The inconsistency in results of the available studies could be attributed to the differences in the inter-societal cultural practices during Ramadan. In addition, duration of fasting and climate variations which are widely variable from one geographic area to another may contribute to the result variations. Migration of Ramadan throughout the seasons

every few years might be an additional contributing factor for the observed outcome variations even in the same geographic area.

The mean INR difference was not affected by the duration of anticoagulation or the total weekly warfarin dose, which have not been addressed in previous studies. The mean difference in the INR level does not seem to be affected by the warfarin adherence scale, which has been noted in previous studies (12). Mean ejection fraction of 51.6±7 (%) and having a majority of patients (66%) in sinus rhythm suggest a relatively low-risk population, which could have happened as a result of excluding the higher risk patients.

Achieving the desired INR level before Ramadan was almost equally feasible in the low and high target INR groups (62.5% and 64.86% respectively) however during Ramadan the low target INR group was more likely to maintain the desired INR level (67.5%) as compared to the high target INR group (51.35%). Although this observation did not reach a statistical significance, it might be clinically relevant and can be attributed to Fasting or other lifestyle changes that occurred during Ramadan.

Seventy-four percent (74%) of patients were within the desired therapeutic range before Ramadan, which has decreased to 66% during Ramadan. Proportion of the out of range INR has increased during Ramadan in both the sub-therapeutic and supra-therapeutic boundaries (figure 2). This effect was more pronounced in the supra-therapeutic direction and almost equally affected the high and low target INR groups (figure 3). This indicates that fluctuations of the INR in both sides of the therapeutic range are exaggerated during Ramadan, which can explain the insignificant difference in the overall mean INR before and during Ramadan.

Study limitations include the retrospective nature of data collection, where some relevant data might be missing or insufficient. In this study, we excluded non-Muslim patients (n=3) and assumed that all Muslim patients were fasting. Results of this study may not be generalizable to many clinical situations that fall under the exclusion criteria, including fasting in-patients. Warfarin administration schedule was not available, as well as the dietary pattern. The time interval between the baseline INR and Ramadan INR readings was variable, which reflects the usual clinical practice.

In conclusion, Ramadan and its associated lifestyle changes in the Saudi community may aggravate the INR fluctuations in warfarin-treated patients. During Ramadan, warfarin-treated patients are more prone to develop supra-therapeutic INR and therefore they deserve careful attention and closer INR monitoring. Prospective studies that should take in consideration detailed data collection of the relevant parameters and avoid the above-mentioned limitations are required to support our observations.

Acknowledgement

The authors would like to extend their special thanks and warm appreciations to the faculty of the research summer school program at KAIMRC for their unlimited support in conducting this study.

Conflict of Interests

The authors declare that they have no conflict of interest in the current study.

Reference

1. Desilver DM. World's Muslim population more widespread than you might think: Pew Research Center; 2017 [updated January 31, 2017]. Available: http:// pewrsr.ch/116QRmk.

2. El-Ashi A. Fasting in Islam: ISlamic Society of Rutgers University. Available from: http://www.eden.rutgers.edu /muslims/fasting.htm.
3. GP Aurigemma BK, WH Gaasch. Antithrombotic therapy in patients with prosthetic heart valves: UpToDate; 2013 [updated Dec 05, 2013]. Available: https://www.uptodate. com/contents/antithrombotic-therapy-for-prosthetic-heart-valves-indications.
4. Holmes MV, Hunt BJ, Shearer MJ. The role of dietary vitamin K in the management of oral vitamin K antagonists. Blood Rev. 2012;26(1):1-14.
5. Addad F, Amami M, Ibn Elhadj Z, Chakroun T, Marrakchi S, Kachboura S. Does Ramadan fasting affect the intensity of acenocoumarol-induced anticoagulant effect? Br J Haematol. 2014;166(5):792-4.
6. Lai YF, Cheen MH, Lim SH, Yeo FH, Nah SC, Kong MC, et al. The effects of fasting in Muslim patients taking warfarin. J Thromb Haemost. 2014;12(3):349-54.
7. Awiwi MO, Yagli ZA, Elbir F, Aglar AA, Guler E, Vural U. The effects of Ramadan fasting on patients with prosthetic heart valve taking warfarin for anticoagulation. J Saudi Heart Assoc. 2017;29(1):1-6.
8. Rifaie O, Sami A, Hamada AH, Ashraf A, Nammas W. Intermittent fasting and laboratory findings in patients with prosthetic valves. Anadolu Kardiyol Derg. 2013;13(2):189.
9. NGHA. Point of Care Services 2014 [updated August 17, 2014]. Available: http://ngha.med.sa/English/Medical Cities/ AlRiyadh/MedicalServices/Lab/Services/Pages/PointofCareS ervices.aspx.
10. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. J Thromb Thrombolysis. 2013;35 (3):312-9.
11. McArthur MC, Dzintars EK, Phillips RB, Bushardt RL. Oral anticoagulation: a review of the current and emerging therapies. JAAPA. 2011;24(11):60-6.
12. Mayet AY. Patient adherence to warfarin therapy and its impact on anticoagulation control. Saudi Pharm J. 2016; 24(1):29-34.

How to cite?

Alghamdi MG, Kokandi AA, Alfadhil RA, Alotaibi LA. Effect of Ramadan Fasting on the International Normalized Ratio in Patients with Mechanical Prosthetic Heart Valves. Ulutas Med J. 2018;4(2):78-84

DOI: 10.5455/umj.20180117091224