

Does fasting during Ramadan influence the therapeutic effect of warfarin?

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Abstract

What is known and objectives: The changes in the therapeutic effect of warfarin during Ramadan fasting are controversial. Hence, we carried out the present study to assess if there are any alterations in the anticoagulation response to warfarin and identify the associated risk factors.

Methods: Patients receiving warfarin for at least 1 year were included in the present study. Their demographic details, warfarin doses, prothrombin time-international normalized ratio (PT-INR) values and concomitant diseases/drugs were retrieved. The dates of Ramadan periods for the calendar years were obtained, and these periods were considered as Ramadan periods. One month before the start dates of Ramadan was considered as pre-Ramadan, and 1 month later than the last dates was considered as post-Ramadan periods. Warfarin sensitivity index (WSI), PT-INR category and time spent in therapeutic range (TTR) were assessed. National Institute of Clinical Health Excellence (NICE) criteria for anticoagulation status were adhered to where TTR (%) <65 was considered as poor anticoagulation.

Results and discussion: One hundred and eighty-three patients were recruited. No significant differences were observed in warfarin doses between the study participants between pre-Ramadan, Ramadan and post-Ramadan periods. Significantly more numbers of PT-INR tests were carried out during Ramadan compared with pre- and post-Ramadan periods. A higher WSI was akin to PT-INR, and lower intra-individual variability was observed in middle-aged and older adults in the post-Ramadan period. Significantly fewer patients had their PT-INR in the therapeutic range and more in the subtherapeutic range during Ramadan periods. Greater proportion of patients had PT-INR in the supratherapeutic range during post-Ramadan periods, particularly the elderly. Although 38.3% had poor anticoagulation status overall, 92.4% met the NICE criteria for poor anticoagulation during the 3 months (pre-Ramadan, Ramadan and post-Ramadan periods).
What is new and conclusion: Ramadan fasting influences the therapeutic effect of warfarin in terms of lowered TTR (%), reduced proportion of patients achieving therapeutic PT-INR and increased risk of poor anticoagulation control. Greater caution is required during the post-Ramadan period, particularly in the elderly category as they are more prone for over-anticoagulation and consequently the risk of bleeding.

KEYWORDS

muslim, oral anticoagulant, pharmacodynamics, Ramadan, religion, warfarin

1 | WHAT IS KNOWN AND OBJECTIVE

Ramadan fasting in Muslims is associated with prolonged daytime fasting and dietary modifications that may influence the therapeutic effect of vitamin K antagonist, warfarin.¹ Fluctuations in the prothrombin time-international normalized ratio (PT-INR) values in patients receiving warfarin have been reported during Ramadan fasting.² Significant increase in the PT-INR values in the supratherapeutic range was observed during Ramadan fasting.³ On the contrary, another report on patients with prosthetic valve replacements on warfarin reported no significant changes in the PT-INR during Ramadan.⁴ Similarly, another study on 18 patients reported a similar PT-INR range during Ramadan, but a greater risk of supratherapeutic anticoagulation was observed in the month following Ramadan.⁵ No significant differences were observed in a 5-year prospective study on 289 patients receiving warfarin.⁶ A report from the Middle East also reports that nearly one-fifth were non-compliant to the prescribed cardiac medications and two-thirds to the dietary instructions during Ramadan period.⁷ Almost all these studies were limited by small sample size; carried out in controlled situations where patients were followed up at weekly intervals deviating from the standard of care; and none assessed the risk factors associated with altered therapeutic effects or did adjust the observed PT-INR to the dose of warfarin that they were administered. Considering the contrasting literature on the effect of Ramadan fasting on the therapeutic effect of warfarin and the above-stated limitations, we conducted the present study to assess the quality of anticoagulation with warfarin during this period.

2 | METHODS

2.1 | Study ethics and study design

The study was initiated following the approval from the relevant Institutional Ethics Committee and Ministry of Health, Kingdom of Bahrain. We carried out the present study as a retrospective cohort study of patients receiving warfarin in a dedicated anticoagulation clinic of the largest tertiary care hospital in Kingdom of Bahrain. Consecutive patients receiving warfarin for at least 1 year were recruited between September 2019 and February 2020.

2.2 | Study procedure

Patients receiving warfarin for at least 1 year were included in the present study. Their demographic details, warfarin doses, PT-INR values and concomitant diseases/drugs were retrieved. The dates of Ramadan

periods for the calendar years were obtained, and these periods were considered as Ramadan periods. One month before the start dates of Ramadan was considered as pre-Ramadan, and 1 month later than the last dates was considered as post-Ramadan periods. CHA_2DS_2-VASc , HAS-BLED and $SAME-TT_2R_2$ scores were assessed for each study participant.^{8,9} Warfarin sensitivity index was calculated as the ratio between the PT-INR measured and the daily dose administered the day before PT-INR measurement.¹⁰ PT-INR was considered as therapeutic if it ranged between 2.5 and 3.5 for patients with heart valve replacements, and 2 and 3 for others. Time spent in therapeutic range (TTR) was assessed using the Rosendaal method.¹¹ The National Institute of Clinical Health Excellence (NICE) criteria for anticoagulation status were adhered, and it was considered poor with TTR <65%.¹² We have compared the anticoagulation status during 3 months (pre-Ramadan, Ramadan and post-Ramadan) with overall anticoagulation from the time of warfarin initiation until their last follow-up with the clinic. Drugs belonging to proton pump inhibitors, statins and amiodarone were considered as potentially interacting drugs with warfarin.

2.3 | Statistical analysis

Descriptive statistics were used for representing demographic characteristics. The Friedman test was used to analyse the differences between numerical variables, and the chi-square tests were used to analyse the differences between categorical variables. Coefficient of variation (CV) for PT-INR and warfarin doses was assessed by the ratio of standard deviations upon average values.¹³ Individuals <40 years were considered young adults, 40-65 as middle-aged and older adults and >65 years as the elderly. Logistic regression analysis was carried out with anticoagulation status (poor/not poor) as dependent variables and the following variables as independent: age category, sex and overall anticoagulation status. Binary logistic regression analyses were also carried out with PT-INR in the therapeutic range during Ramadan and the supratherapeutic range in the post-Ramadan periods with age group, sex and presence of a drug with potential interaction as the dependent variables. Odds ratio (OR) with 95% confidence intervals was used for assessing the risk of categorical outcomes. All the statistical tests were carried out using SPSS version 26 (IBM Corp. Released 2018. IBM SPSS Statistics for Windows, Version 26.0.: IBM Corp.).

3 | RESULTS

3.1 | Demographic details

One hundred and eighty-three patients were recruited, and a summary of their demographic characteristics is provided in Table 1. One

hundred and thirty-three patients (72.7%) received one or more of the drugs interacting with warfarin, namely statins (117, 63.9%), proton pump inhibitors (68, 37.2%), amiodarone (6, 3.3%) and carbamazepine (2, 1.1%).

3.2 | Warfarin doses during pre-Ramadan, Ramadan and post-Ramadan periods

Median (range) numbers of periods of Ramadan amongst the study participants were 2 (1-8), and a total of 410, 434 and 430 dosing periods were available for comparison in the pre-Ramadan, Ramadan and post-Ramadan periods. No significant differences were observed in the warfarin doses between these periods (Table 2).

3.3 | PT-INR and TTR (%) during pre-Ramadan, Ramadan and post-Ramadan periods

Total numbers of PT-INR tests was significantly higher during Ramadan period compared with pre-Ramadan and post-Ramadan periods in the entire study population, the middle-aged and older adults, and the elderly age groups (Table 2). Comparison of PT-INR and TTR (%) in the study population and different age groups

is represented in Table 3. PT-INR was significantly higher in the post-Ramadan period compared with pre-Ramadan and Ramadan periods in middle-aged and older adults. However, no significant difference was observed in the proportion of patients with subtherapeutic, therapeutic and supratherapeutic categories of PT-INR between the study participants (Figure 1). Significantly fewer patients were observed to reach therapeutic range (pre-Ramadan: 241/302, 79.8%; Ramadan: 211/299, 70.6%; and post-Ramadan: 212/294, 72.1%) and more were observed to reach subtherapeutic (pre-Ramadan: 35/302, 11.6%; Ramadan: 51/299, 17.1%; and post-Ramadan: 36/294, 12.2%) range during Ramadan month. Similarly, more PT-INR values were observed in supratherapeutic range (Pre-Ramadan: 26/302, 8.6%; Ramadan: 37/299, 12.4%; and post-Ramadan: 46/294, 15.6%) in the post-Ramadan periods. The elderly had an increased risk of achieving PT-INR in the supratherapeutic range compared with other age groups (OR: 2.4; 95% CI: 1.1, 5.6).

Lower TTR (%) was observed during the 3 months (pre-Ramadan, Ramadan and post-Ramadan periods) (Table 3). No significant differences were observed in the TTR (%) over 3 months between the different age groups of the study participants.

3.4 | WSI during pre-Ramadan, Ramadan and post-Ramadan periods

Table 4 represents the WSI and per cent changes in WSI between various age groups of the study participants. Significantly higher WSI was observed in the post-Ramadan period compared with pre-Ramadan and Ramadan periods in the middle-aged and older adults.

3.5 | Intra-individual variability of warfarin doses, PT-INR and WSI

The CVs for warfarin doses, PT-INR and WSI are represented in Table 5. Statistically significantly lower CV was observed for PT-INR during Ramadan period for middle-aged and older adults.

3.6 | Proportion of patients with poor anticoagulation and associated factors

Overall assessment of PT-INR revealed that 70 of 183 (38.3%) met the criteria for poor anticoagulation. Surprisingly, 158 (92.4%) had poor anticoagulation status during the 3 months (pre-Ramadan, Ramadan and post-Ramadan periods), whereas 13 (7.6%) did not. Logistic regression analysis revealed no significant association between age, sex, presence of any drugs with potential interaction, overall anticoagulation status and anticoagulation status during the three periods (Pre-Ramadan, Ramadan and post-Ramadan). None of the patients reported any bleeding episodes during these 3 months.

TABLE 1 Demographic details of the study participants (N = 183)

Parameters	Values
Age (years) ^a	66.6 (13.7)
Male: Female	1:1
Body weight (kg) ^a	75.3 (17.7)
Prior duration of warfarin therapy (days) ^a	1043.4 (570.5)
CHA ₂ DS ₂ -VASc score ^a	3.7 (1.5)
HAS-BLED score ^a	2.3 (1.2)
SAMe-TT2R2 score ^a	1.4 (0.6)
Concomitant diagnoses (n)	
Systemic hypertension	109
Diabetes mellitus	80
Atrial fibrillation/Atrial flutter	80
IHD	38
Thyroid disorders	22
Heart valve disorders	16
Rheumatoid arthritis/SLE	11
Stroke	7
CKD	7
CCF	7
Bronchial asthma	7

Abbreviations: CCF, congestive cardiac failure; CKD, chronic kidney disease; IHD, ischaemic heart disease; SLE, systemic lupus erythematosus.

^aRepresented in mean (SD).

TABLE 2 Comparison of warfarin doses and number of PT-INR values in the pre-Ramadan, Ramadan and post-Ramadan periods

Age groups	Mean (SD) warfarin doses (mg/day)			P-values
	Pre-Ramadan	Ramadan	Post-Ramadan	
Study population (N = 183)	4.8 (2.3)	4.8 (2.6)	4.8 (2.2)	.2
Young adults (n = 11)	5.2 (1.4)	5.4 (1.4)	5.4 (1.5)	.3
Middle-aged and older adults (n = 64)	5 (2.2)	5.2 (3.1)	5 (2.2)	.2
Elderly (n = 108)	4.7 (2.4)	4.6 (2.3)	4.6 (2.2)	.5
Age groups	Mean (SD) number of PT-INR values			P-values
	Pre-Ramadan	Ramadan	Post-Ramadan	
Study population (N = 183)	1.1 (0.9)	1.6 (1)	1.1 (0.7)	.0001*
Young adults (n = 11)	1.5 (1.3)	1.8 (1.3)	1.1 (0.6)	.2
Middle-aged and older adults (n = 64)	1 (0.9)	1.5 (1)	1 (0.7)	.0001*
Elderly (n = 108)	1.2 (0.9)	1.5 (1)	1.1 (0.7)	.0001*

*Statistically significant.

TABLE 3 Comparison of PT-INR and TTR in pre-Ramadan, Ramadan and post-Ramadan periods

Age groups	PT-INR				P-values	TTR (%)	
	Pre-Ramadan	Ramadan	Post-Ramadan	Over 3-month period		P-values	
Study population (N = 183)	2.4 (0.5)	2.5 (0.5)	2.5 (0.6)	.4	36.8 (21)	NA	
Young adults (n = 11)	2.3 (0.5)	2.9 (1.9)	2.5 (0.5)	.4	35.7 (18.2)	.7	
Middle-aged and older adults (n = 64)	2.5 (0.5)	2.5 (0.5)	2.6 (0.8)	.008*	36.7 (22.2)		
Elderly (n = 108)	2.4 (0.5)	2.4 (0.6)	2.5 (0.6)	.6	37 (20.5)		

Abbreviations: NA, not assessable; PT-INR, prothrombin time-international normalized ratio; TTR, time spent in therapeutic range.

*Statistically significant.

4 | DISCUSSION

We evaluated the therapeutic effect of warfarin during the 3 months related to Ramadan fasting in 183 patients. No significant differences were observed in warfarin doses between the study participants between pre-Ramadan, Ramadan and post-Ramadan periods. Significantly more numbers of PT-INR tests were carried out during Ramadan compared with pre- and post-Ramadan periods. A higher WSI was akin to PT-INR, and lower intra-individual variability was observed in middle-aged individuals in the post-Ramadan period. Significantly fewer patients were observed in the therapeutic range and more in the subtherapeutic range during Ramadan. Also, significantly higher proportion of patients was observed in the supratherapeutic range during post-Ramadan period, particularly the elderly. Although 38.3% had poor anticoagulation status overall, 92.4% met the NICE criteria for poor anticoagulation during pre-Ramadan, Ramadan and post-Ramadan periods.

Studies assessing the effect of Ramadan fasting on warfarin are limited. A recent study from Turkey in just 18 patients observed no significant change either in the warfarin doses or in the PT-INR during Ramadan period and increased tendency to achieve supratherapeutic range subsequently.⁵ Additionally, the authors

have also observed greater proportion of patients in the therapeutic range during Ramadan. Although our results are similar to this study, we did not observe an increased proportion of patients in the therapeutic range during Ramadan month. On the other hand, a decrease in the proportion of patients with therapeutic PT-INR and more in the subtherapeutic category was observed in the Ramadan period by Lai et al³ similar to the present study. One possible reason for this could be the drug-food interaction due to change in the dietary patterns as observed in several other studies where there is an altered consumption of vegetables, legumes and dairy products during Ramadan fasting.¹⁴ A higher intake of vitamin K, total fibre, iron, manganese, magnesium, β -carotene, folate, vitamin B₁₂, potassium and calcium was observed during Ramadan fasting.¹⁵ Even the dietary recommendations from World Health Organization during Ramadan fasting include green salads or vegetables of patient's choice.¹⁶ However, until now there is no published consensus on the dietary recommendation for patients receiving warfarin. We also observed a higher WSI and consequently a higher proportion of patients in the supratherapeutic range in the post-Ramadan period. This calls for a close attention and intense follow-up of patients from the last week of Ramadan fasting to reduce their risk of over-anticoagulation and bleeding.

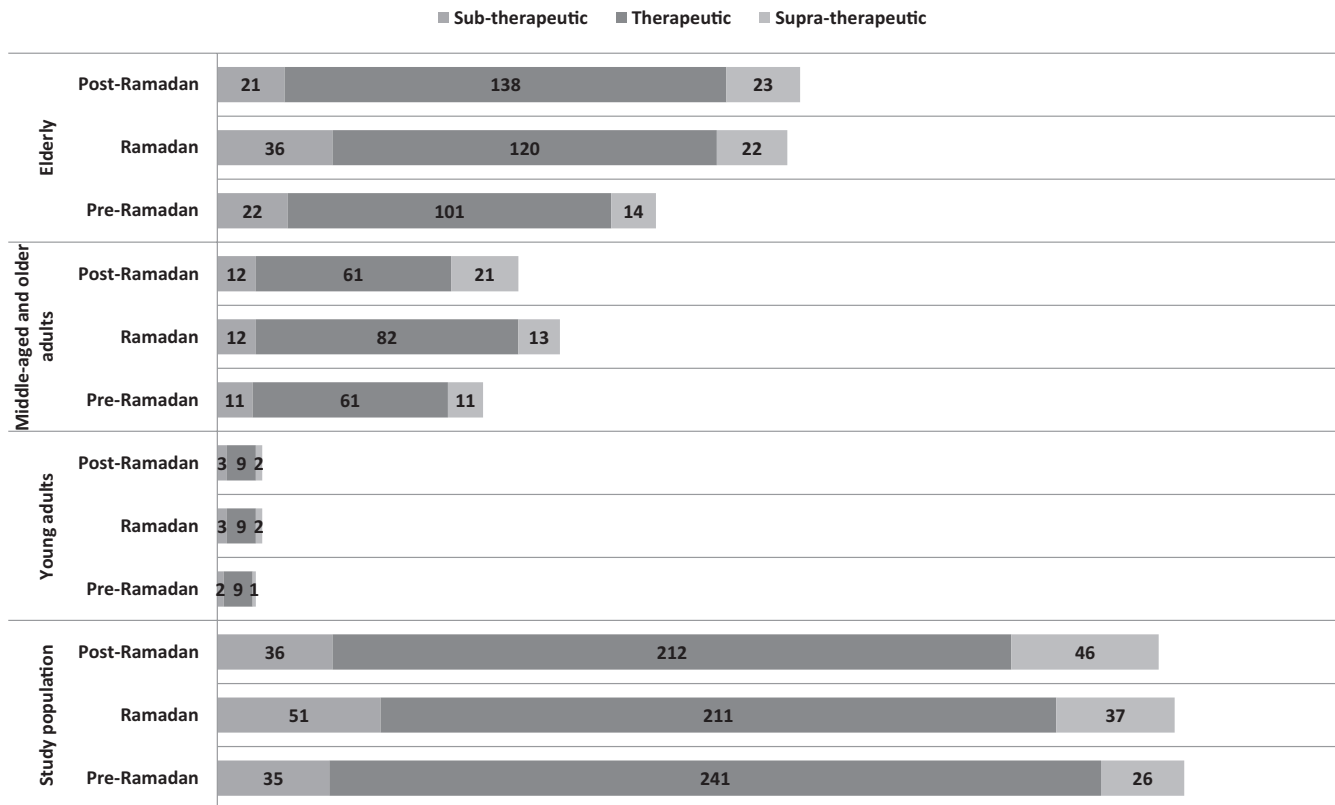


FIGURE 1 Comparison of numbers of patients in the subtherapeutic, therapeutic and suprathreshold categories of PT-INR. Significantly fewer patients were observed to reach therapeutic range during Ramadan and more achieving suprathreshold range in the post-Ramadan periods

TABLE 4 Comparison of warfarin sensitivity index in the study participants

Age categories	Pre-Ramadan	Ramadan	Post-Ramadan	P-values
WSI				
Study population (N = 183)	0.6 (0.4)	0.6 (0.4)	0.7 (0.5)	.3
Young adults (n = 11)	0.5 (0.2)	0.4 (0.1)	0.5 (0.3)	.4
Middle-aged and older adults (n = 64)	0.6 (0.4)	0.6 (0.5)	0.7 (0.4)	.003*
Older adults (n = 108)	0.6 (0.4)	0.7 (0.4)	0.7 (0.5)	.6
	Pre-Ramadan vs Ramadan	Ramadan vs Post-Ramadan	Post-Ramadan vs Pre-Ramadan	
Per cent change in WSI				
Study population (N = 183)	3.3 (27.6)	10.4 (56.3)	9.4 (32.2)	.3
Young adults (n = 11)	3.8 (30.9)	7.6 (36)	14.5 (38.2)	.6
Middle-aged and older adults (n = 64)	3.8 (27.4)	21.8 (88.8)	10.8 (28.4)	.02*
Elderly (n = 108)	3 (27.8)	4.3 (25.9)	8.1 (33.7)	.9

*Statistically significant.

We have identified that this risk is higher with the elderly. We observed that the elderly on oral anticoagulants had better quality of life and were more likely to be compliant to the prescribed regimen.¹⁷ Variable consumption of vitamin K-rich foods has been observed in the elderly, and more evidence is emerging relating reduced vitamin K intake to bone health and physical decline in this age group.¹⁸ More research is needed to identify the factors

associated with dietary behaviour in this subpopulation that may influence therapeutic effect of warfarin, particularly during Ramadan and post-Ramadan periods.

Despite being retrospective, the present study has identified changes in the therapeutic effect following the administration of warfarin and has identified certain groups with higher risk of abnormal anticoagulation. A limitation was that we could not assess the

TABLE 5 Intra-individual variability in the warfarin doses, PT-INR, TTR (%) and WSI

Age categories	Warfarin doses			PT-INR			WSI			P-values
	Pre-Ramadan	Ramadan	Post-Ramadan	Pre-Ramadan	Ramadan	Post-Ramadan	Pre-Ramadan	Ramadan	Post-Ramadan	
Study population (N = 183)	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)	.6
Young adults (n = 11)	0.1 (0.1)	0.04 (0.05)	0.08 (0.08)	0.3 (0.02)	0.2 (0.2)	0.2 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)	.4
Middle-aged and older adults (n = 64)	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)	0.2 (0.1)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.2)	0.2 (0.1)	.03*
Elderly (n = 108)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)	.3

*Statistically significant.

dietary lifestyle and the extent of fasting. To conclude, fasting during Ramadan is likely to influence therapeutic effect of warfarin in terms of lowed TTR (%), reduced proportion of patients achieving therapeutic PT-INR and increased risk of poor anticoagulation. Greater caution is required during the post-Ramadan period, particularly in the elderly category as they are more likely to be over-anticoagulated.

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CONFLICT OF INTEREST

None.

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