

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

Yasser H. Abdelrahman, Saad M. Ammar, Mohamed Z. El-morshedy, Mahmoud Sh. Abdelmoneum

Department of cardiovascular medicine, Benha faculty of medicine, Benha University, Egypt.

Correspondence to: Mohamed Z. El-morshedy, Department of cardiovascular medicine, Benha faculty of medicine, Benha University, Egypt.

Email: morshedyzaki86@gmail.com

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Abstract

Background: Ramadan fasting presents unique challenges for patients with mechanical prosthetic heart valves on Warfarin therapy. **This study aimed to** evaluate the potential effects of Ramadan fasting and lifestyle changes during Ramadan on the International Normalized Ratio (INR) level in patients using Vitamin K anticoagulant VKA (Warfarin) for mechanical prosthetic heart valves as anticoagulation. **Methods:** This prospective study included 150 Muslim patients with mechanical prosthetic heart valves, tracking their INR levels over a period encompassing the month of Ramadan. Patients underwent regular assessments, including clinical examinations, INR measurements, and echocardiography. Data were collected on medication regimens, Warfarin intake timing, and fasting adherence. **Results:** The mean INR levels increased during Ramadan, with the most significant rise occurring in the last two weeks. Patients exhibited a significantly higher mean INR during Ramadan compared to the pre-Ramadan and post-Ramadan periods. Importantly, more patients reached the supra-therapeutic INR range during Ramadan, while fewer were within the sub-therapeutic range when compared to the post-Ramadan phase. **Conclusion:** Ramadan fasting can lead to significant fluctuations in INR

levels in patients with mechanical prosthetic heart valves using Warfarin. Careful monitoring and adjustment of anticoagulation therapy may be necessary to maintain therapeutic INR ranges during this religious observance.

Keywords: Ramadan Fasting; International Normalized Ratio; Mechanical Prosthetic Heart Valves; Warfarin; Anticoagulation Therapy.

Introduction

Around the world, a Muslim population of more than 1.6 billion performs an obligatory religious act of Fasting (Siam) during the Holy month of Ramadan, which corresponds to the 9th month of the Hijra Calendar, Religious fasting includes abstinence from food and drinks from dawn to dusk. During Ramadan, a lot of Muslim societies undergo significant lifestyle modifications, including dietary patterns. These dietary modifications, along with the prolonged day-time fasting and medication scheduling changes- may adversely affect the anticoagulation status of patients using Vitamin K Antagonist (VKA) (1).

Despite the recent advances in the field of oral anticoagulants, VKA remains the standard and most effective and reliable oral anticoagulant used in mechanical prosthetic heart valve patients (2).

The choice of an initial dose, and its conversion to a maintenance dose, is traversed by the delay in response (1-3 days), the wide variation between individuals, and the lack of a close relationship between serum warfarin concentration and response (3). Several authors have published predictive schedules for dosing based on International Normalized Ratio (INR) measurements in the first 2 days of treatment, but these have proved to be of only limited benefit and the most common method is still to 'try it, and see' (4). However, due to its small therapeutic window and its potential interactions with food and medications,

regular monitoring and dose adjustments are required. The potential influence of a person's dietary pattern on VKA's therapeutic effect has raised the question of whether intermittent, periodic fasting, as practiced in some religions, will affect an individual's anticoagulation therapy (5, 6).

Available studies on the effect of Fasting on the INR- were conducted in different geographic areas of the world. These studies included diverse patient populations with widely variable cultural & social backgrounds and ended up with inconsistent results (7).

Our study came to evaluate this unresolved issue in the Egyptian community, using a larger sample size of a more homogeneous population.

We aimed in this study to evaluate the potential effects of Ramadan fasting and lifestyle changes during Ramadan on the INR level in patients using Vitamin K anticoagulant VKA (Warfarin) for mechanical prosthetic heart valves as anticoagulation.

Patients and methods

This prospective study included 150 Muslim patients with mechanical prosthetic heart valves attending for follow-up at the outpatient clinic at Mahalla Cardiac Center and Benha Univeresity Hospital during the month of Ramadan 1440 (Islamic Hijra Calendar) corresponding to the period from 6 May to 4 June 2019. The approval of the ethical committee "Approval code:

MD.10.5.2019” and obtaining an informed written consent from the study participants- male and females who were 18 years of age or older- and have had a single or double mechanical prosthetic heart valve at any valve position who were using Warfarin and able to fast- were eligible for inclusion in this study.

Inclusion criteria were patients with a single or double mechanical prosthetic heart valve at any valve position who were utilizing warfarin as their anticoagulant and were in a clinically stable condition. Additionally, eligible participants needed to be capable of fasting.

Exclusion criteria were patients with significant baseline INR fluctuations, those experiencing anticoagulation interruptions or non-compliance, individuals with chronic liver or renal disease, advanced malignancies, acute heart failure decompensation, non-fasting patients, or those deemed medically unfit to fast, as well as those who recently underwent antibiotic treatment, were hospitalized for cardiac or non-cardiac reasons, experienced recent thromboembolic or hemorrhagic events, or had undergone recent major surgical operations.

Methods:

All patients in this study were subjected to:

A multi-stage assessment of patients. At the initial visit before Ramadan, patients' demographic information and medical history were recorded, including risk factors like hypertension, diabetes mellitus,

rheumatic fever history, and medication use. A thorough clinical examination was conducted, encompassing general and local heart examinations. Subsequently, a schedule of at least six follow-up visits was established, with one visit in the pre-Ramadan month, four weekly visits during Ramadan, and one post-Ramadan visit over three months.

Each visit included an electrocardiograph (ECG) to detect abnormalities, such as ischemia, heart failure, or arrhythmias, and laboratory assessments, with multiple INR readings taken. Patients were monitored for signs of major bleeding or thrombotic events, adherence to warfarin, and medication adjustments. Additionally, all patients underwent echocardiography before and after Ramadan to assess prosthetic valve function and left ventricular systolic and diastolic functions.

Medications

Time of Warfarin: All patients had been advised to take warfarin more than 4 hours from iftar and no food Intake at least 2 hours after Warfarin ingestion. Mostly Warfarin intake was within a period between 11 pm and 1 am.

Missed Doses of Warfarin: All patients had been advised to take warfarin regularly and if any patient forgets to take it, the patient must take it once he remembers if it is still before dawn. and all patients had been asked to report this.

Intentional Omission of Warfarin: All patients had been advised not to skip or omit any warfarin dose for any reason. And

if there are any indications for that, the patient must consult before that.

Other Medications: All other medications for patients had been recorded with no specific adjustment being made except according to their vital data and clinical status. All patients had been given specific instructions to take their medications around both meals (iftar and suhur) far from warfarin.

International Normalization Ratio:

INR Measurement: All INR measurements had been done at Mahalla Cardiac Centre Main Laboratory using the Stago STA Compact CT Coagulation System Device. The INR test had been done from 08.00 am to 11.00 am, about at least 8 hours after the last warfarin dose and at least 5 hours after the last meal (Suhur), **Figure (1).**

INR Range:

In our study, two therapeutic INR ranges were employed: a high range of 2.5 to 3.5 for patients with prosthetic mitral valves or prosthetic aortic valves with additional thromboembolism risk factors, such as atrial fibrillation or previous thrombosis. The INR results below 2.5 were considered sub-therapeutic, while those above 3.5 were considered supra-therapeutic. For other patients with prosthetic aortic valves and no additional risk factors, a low therapeutic range of 2.0 to 3.0 was utilized. INR results below 2.0 were considered sub-therapeutic, and those above 3.0 were considered supra-therapeutic.

Fasting:

All patients in the study completed fasting for the entire month of Ramadan, which lasted approximately 16 hours daily. They were regularly asked to confirm their fasting status during each visit.

Clinical Outcomes:

The primary study outcome focused on the mean change in INR levels during Ramadan compared to periods before and after Ramadan. Clinical endpoints for patient participation termination included venous or arterial thrombotic events or major bleeding, defined by standard criteria used in clinical trials. Patients could be excluded from the study at any time if they were unable to fast for any reason.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test and ANOVA (F) test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results

Within the study populations, there were 105 patients (70% of all patients) who had a mitral valve prosthesis, 19 patients

(12.7%) who had aortic valve prosthesis, while there were 26 patients (17.3%) who had both mitral valve and aortic valve prosthesis. Regarding comorbidities, 49 patients (32.7%) had AF as the most common medical disease among the study population, 11 patients (7.3%) had hypertension, the same percentage with diabetes, while there were 4 patients (2.7%) did PCI. Beta blocker was the most common medication used among the study population as it had been used by 73 patients (48.7%), followed by diuretics which were used by 61 patients (40.7%), digoxin has been used by 41 patients (27.3%), ACE inhibitors have been used by 23 patients (15.3%), 10 patients (6.7%) used Insulin, 5 patients (3.3%) used aspirin, the same as ARBs and statin, 3 patients (2.0%) had nitrates within their treatment, only one patient (0.7%) using clopidogrel, **Table (1)**.

Warfarin treatment among the study populations, with the dose of warfarin ranging from 1.0 mg to 11.0 mg, and the mean dose within the study was (4.86 ± 1.84) mg. The mean duration of warfarin treatment was (8.20 ± 5.83) years with a minimum duration of about 6 months, and a maximum duration of treatment was 23 years. Regarding the classifications of the study population according to INR target range, there were 16 patients (10.7%) with a low INR target range (2.0:3.0) who had aortic valve prosthesis without other risk factors for thromboembolism, and there were 134 patients (89.3%) with a high INR target range (2.5:3.5) who had mitral valve prosthesis or other aortic valve prostheses

with risk factors for thromboembolism, **Table (2)**.

The mean INR during Ramadan month was significantly higher compared to pre-Ramadan, (2.86 ± 0.47) in Ramadan vs 2.71 ± 0.47 in pre-Ramadan, P-value $<0.001^*$. Also, mean INR during Ramadan month was significantly higher compared to the post-Ramadan period (2.86 ± 0.47) in Ramadan vs 2.77 ± 0.47 in post-Ramadan, P-value $<0.001^*$). While there was a mild statistically significant increase of mean INR in the post-Ramadan period compared to the pre-Ramadan Period (2.77 ± 0.47) in post-Ramadan vs 2.71 ± 0.47 in pre-Ramadan, P-value $=0.049^*$), **Table (3)**.

There was a progressive increase in mean INR throughout the four weeks of Ramadan with a statistically significant increase in mean INR results between all four weeks. The mean INR for the patients in the first week was (2.75 ± 0.50) which increased by 0.06 to reach (2.81 ± 0.48) during the second week, then it increased again by 0.10 and 0.06 during the third and fourth weeks to achieve mean INR (2.91 ± 0.47) and 2.97 ± 0.48 respectively), **Table (4)**.

Distribution of the studied patients according to INR target range were shown in **Table (5)** and **Figure (2)**.

There was no statistical difference in the proportion of patients within the therapeutic INR target range between all the three study periods (64.7% of all INR values obtained in the pre-Ramadan period were within the therapeutic target range,

the same percentage during Ramadan, it was 58.7% in post-Ramadan). Significantly more patients were observed to reach the Supra-therapeutic INR range during Ramadan month compared to pre-Ramadan (24 patients during Ramadan vs. 15

patients pre-Ramadan, $p=0.012$), and significantly fewer patients were observed within the sub-therapeutic INR range in Ramadan compared to post-Ramadan (29 patients during Ramadan vs. 43 patients post-Ramadan, $p=0.011$), **Table (6)**.

Table 1: Demographic characteristics, type of prosthetic Valve, Co-Morbidities and medications of the studied population.

Population		N (150)
Gender	Male	42 (28%)
	Female	108 (72%)
Age (/years)	Mean \pm SD.	42.49 \pm 10.96
	Min. – Max.	19.0 – 67.0
Type of Valve		
Aortic Valve Prosthesis		19 (12.7%)
Mitral Valve Prosthesis		105 (70%)
Double Valve Prosthesis		26 (17.3%)
Co-Morbidities		
AF		49 (32.7%)
DM		11 (7.3%)
HTN		11 (7.3%)
Percutaneous Coronary Intervention (PCI)		4 (2.7%)
Medications		
ACEI		23 (15.3%)
ARBs		5 (3.3%)
Aspirin		5 (3.3%)
Beta Blockers		73 (48.7%)
Clopidogrel		1 (0.7%)
Digoxin		41 (27.3%)
Diuretic		61 (40.7%)
Insulin		10 (6.7%)
Nitrate		3 (2.0%)
Statin		5 (3.3%)

AF: Atrial Fibrillation, DM: Diabetes Miletus, HTN: Hypertension, PCI: Percutaneous Coronary Intervention, ACEI: Angiotensin-Converting Enzyme Inhibitors, ARBs: Angiotensin II Receptor Antagonists

Table 2: Warfarin treatment and the target INR range of the study population.

Warfarin	Min. – Max.	Mean \pm SD.	Median (IQR)
Dose (mg)	1.00 – 11.00	4.86 \pm 1.84	5.00 (3.50 –6.0)
Duration (years)	0.50 – 23.00	8.20 \pm 5.83	7.50 (3.0 –12.0)
Target INR Range		Number of patients	Percentage
Low (2.0:3.0)		16	10.7%
High (2.5:3.5)		134	89.3%

Table 3: Comparison between the three studied periods according to mean INR.

INR	Min. – Max.	Mean ± SD.	Median (IQR)
Pre-Ramadan	1.64 – 4.00	2.71 ± 0.47	2.63 (2.40 –3.0)
During Ramadan	1.77 – 4.06	2.86 ± 0.47	2.76 (2.56 –3.13)
Post-Ramadan	1.73 – 4.00	2.77 ± 0.47	2.70 (2.40 –3.10)
F		28.679*	
p		<0.001*	
Significance between periods.	p ₁ <0.001*	p ₂ =0.049*	p ₃ <0.001*

F: F test (ANOVA) with repeated measures, Sig. bet. periods were done using **the Post Hoc Test (adjusted Bonferroni)**, **p**: p-value for comparing the three studied periods, **p₁**: p-value for comparing between **Pre-Ramadan** and **During Ramadan**, **p₂**: p-value for comparing between **Pre-Ramadan** and **Post-Ramadan**, **p₃**: p-value for comparing between **During Ramadan** and **Post-Ramadan**, *: Statistically significant at p ≤ 0.05

Table 4: Comparison between the four weeks of Ramadan according to mean INR.

INR	Min. – Max.	Mean ± SD.	Median (IQR)
1 st week	1.71 – 4.10	2.75 ± 0.50	2.70 (2.40 –3.10)
2 nd week	1.70 – 4.00	2.81 ± 0.48	2.80 (2.50 –3.10)
3 rd week	1.70 – 4.10	2.91 ± 0.47	2.83 (2.60 –3.20)
4 th week	1.70 – 4.20	2.97 ± 0.48	2.90 (2.66 –3.26)
F		81.145*	
p		<0.001*	
Significance between periods.	p ₁ <0.001* p ₄ <0.001*	p ₂ <0.001* p ₅ <0.001*	p ₃ <0.001* p ₆ <0.001*

F: F test (ANOVA) with repeated measures, Sig. bet. periods were done using **the Post Hoc Test (adjusted Bonferroni)**, **p**: p-value for comparing the three studied periods, **p₁**: p-value for comparing between **1st week** and **2nd week**, **p₂**: p-value for comparing between **1st week** and **3rd week**, **p₃**: p-value for comparing between **1st week** and **4th week**, **p₄**: p-value for comparing between **2nd week** and **3rd week**, **p₅**: p-value for comparing between **2nd week** and **4th week**, **p₆**: p-value for comparing between **3rd week** and **4th week**, *: Statistically significant at p ≤ 0.05.

Table 5: Distribution of the studied patients according to INR target range.

	Subtherapeutic		Therapeutic		Supra therapeutic	
	No.	%	No.	%	No.	%
Pre-Ramadan	38	25.3%	97	64.7%	15	10.0%
During Ramadan						
1 st week	43	28.7%	88	58.7%	19	12.7%
2 nd week	34	22.7%	97	64.7%	19	12.7%
3 rd week	15	10.0%	111	74.0%	24	16.0%
4 th week	15	10.0%	109	72.7%	26	17.3%
Mean	29	19.3%	97	64.7%	24	16.0%
Post-Ramadan	43	28.7%	88	58.7%	19	12.7%
Total	188	20.9%	590	65.6%	122	13.6%

Table 6: Comparison between the three studied periods according to INR therapeutic ranges.

INR	Pre-Ramadan	During Ramadan	Post-Ramadan	p ₁	p ₂	p ₃
Subtherapeutic	38 (25.3%)	29 (19.3%)	43 (28.7%)	0.078	0.441	0.011*
Therapeutic	97 (64.7%)	97 (64.7%)	88 (58.7%)	1.000	0.212	0.188
Supratherapeutic	15 (10.0%)	24 (16.0%)	19 (12.7%)	0.012*	0.424	0.227

Data were expressed using Number (%), p₁: p-value for McNemar test for comparing between Pre-Ramadan and During Ramadan, p₂: p-value for McNemar test for comparing between Pre-Ramadan and Post-Ramadan, p₃: p-value for McNemar test for comparing between During Ramadan and Post-Ramadan, *: Statistically significant at p ≤ 0.05.

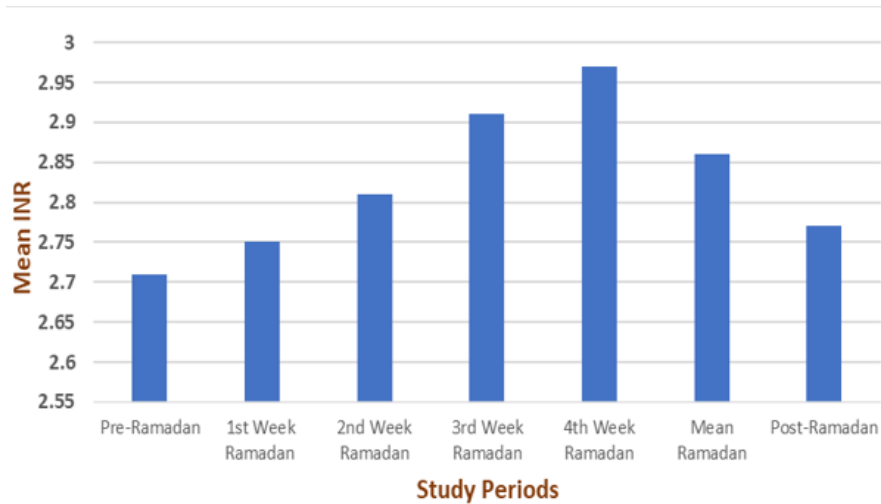


Fig. 1: Mean INR of the studied patients within the study periods.

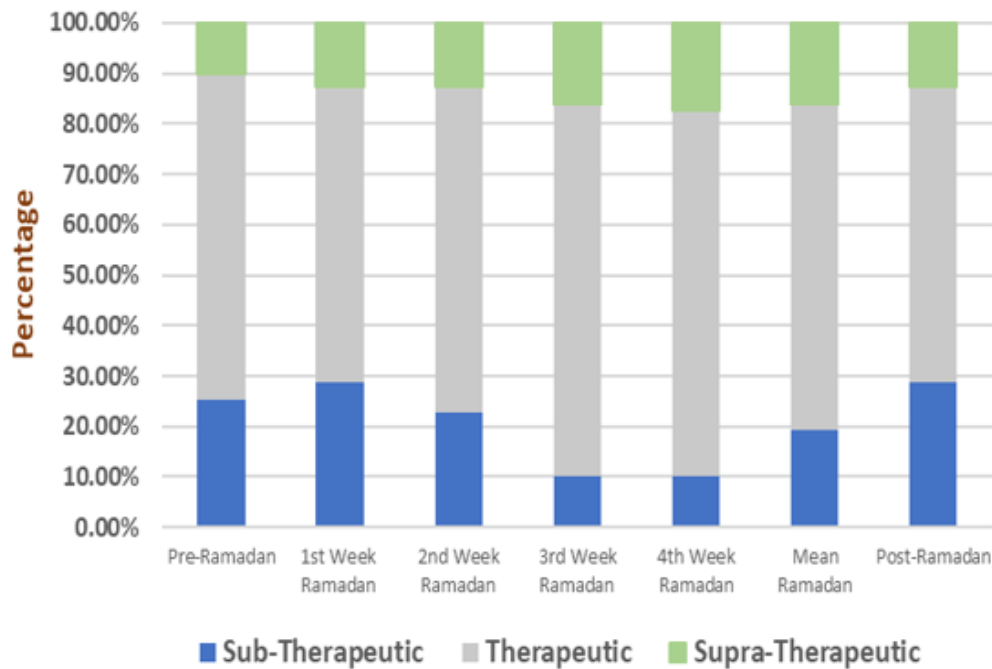


Fig. 2: Distribution of the studied population according to INR ranges.

Discussion

We aimed to evaluate the potential effects of fasting and lifestyle changes during Ramadan on the INR level in patients using Warfarin (VKA) for mechanical prosthetic heart valve as anticoagulation and evaluate this unresolved issue in the Egyptian community, using a larger sample size of a more homogeneous population.

A total of 150 patients were included in this prospective study, of them there were 42 males (28%) and 108 females (72%), with ages ranging between (19-67) years with a mean age of about (42±11) years, Table (1), Figure (3). Of them, there were 23 patients (15.3%) had their first Ramadan after the valve operation, Table (5).

In agreement with our study, a study reported the findings of their prospective study on the effects of Ramadan fasting on a group of 32 Muslim patients taking warfarin at Singapore General Hospital- they found a statistically significant increase in the mean INR during Ramadan month compared to both Pre-Ramadan and Post-Ramadan periods (mean INR was 2.67 during Ramadan vs. 2.44 before Ramadan; $P = 0.006$, Increased by 0.23 while, it was 2.67 during Ramadan vs. 2.38 after Ramadan; $P < 0.001$, Increased by 0.29) (5).

In contrast to our study, a study observed no significant difference between non-Ramadan months, with mean INR values being similar pre-Ramadan (2.44) and

post-Ramadan (2.38; $P = 1.000$). They attributed these findings to dietary factors, changes in sleep patterns, and shifts in meal & medication timing. However, their study had limitations, including a small sample of 32 patients in the Far East, predominantly using warfarin for non-valve-related conditions, with the majority having venous thromboembolism (84.3%) or atrial fibrillation (9.4%), and only 6.3% with mechanical valve replacements (2).

A study found that INR values experienced a significant acute increase during the first 2 weeks of Ramadan, with INR2 (4.1 ± 1.7) significantly higher than INR1 (2.9 ± 0.8 ; $P < 0.0001$). About 37.3% of patients had INR2 > 4.5 and were excluded. A similar INR increase was observed in the last 2 weeks of Ramadan, with INR3 (3.4 ± 0.88) significantly higher than INR2 ($P < 0.0001$), leading to another 11.9% of patients reaching INR3 > 4.5 . They attributed this increase to dietary changes during Ramadan, potentially affecting VKA metabolism (8).

Additionally, a study in Turkey with 18 patients with prosthetic valves, observing INR changes during Ramadan. They reported insignificant differences in mean INR values during Ramadan compared to pre-Ramadan (2.67 vs. 2.47; $p = 0.183$) but found a significant increase post-Ramadan (3.05 vs. 2.47; $p = 0.004$). The authors noted a progressive INR increase throughout the study and found an insignificant difference between post-Ramadan and Ramadan (3.05 vs. 2.67; $p =$

0.059), contrasting with your results and the result is reported a significant decrease in mean INR values post-Ramadan compared to Ramadan (9).

Two studies, including one conducted in 2020; Sridharan., et al (10), and a prospective study in Egypt; Rifaie et al., (11)- found no significant changes in mean INR values during, before, or after Ramadan, contrary to prior research. There was a retrospective study included 183 patients in Bahrain and didn't identify any significant differences in mean INR across pre-Ramadan, Ramadan, and post-Ramadan periods, with a limitation being its retrospective design. Also, another's prospective study enrolled 70 patients with mechanical bileaflet prostheses who were prescribed warfarin, and they observed no significant difference in INR values between fasting during Ramadan and non-fasting after Ramadan (11).

Our study revealed that during Ramadan, a lower percentage of patients had sub-therapeutic INR results (19.3%) compared to pre-Ramadan (25.3%) and post-Ramadan (28.7%), with a significant difference observed in sub-therapeutic cases between Ramadan and post-Ramadan (29 patients in Ramadan vs. 43 in post-Ramadan; P-value=0.011). Moreover, during Ramadan, a higher percentage of patients experienced supra-therapeutic INR results (16.0%) compared to post-Ramadan (12.7%) and pre-Ramadan (10.0%), with a statistically significant difference in supra-therapeutic cases between Ramadan and pre-Ramadan (24 patients in Ramadan vs. 15 in pre-

Ramadan; P-value=0.012). This pattern indicates fluctuations in INR levels during and after Ramadan, with fewer patients within the sub-therapeutic range during Ramadan, but more within the supra-therapeutic range, and the opposite trend post-Ramadan.

In line with our findings, a study Lai et al., (5) reported a decrease in the time within the therapeutic range (TTR) during Ramadan, accompanied by an increase in TTR above the therapeutic range. The percentage of TTR decreased from 80.99% pre-Ramadan to 69.56% during Ramadan (P=0.453), while the time above the range increased from 10.80% pre-Ramadan to 29.87% during Ramadan (P=0.027), and time below the range increased from 0.57% during Ramadan to 15.49% post-Ramadan (P=0.006). However, a study of Awiwi et al., (9), while contradicting our results regarding INR changes during Ramadan, noticed fluctuations in the quality of anticoagulation throughout their study, with the largest fluctuation in the ratio of patients with optimal therapeutic anticoagulation observed between Ramadan and the first week post-Ramadan (87.5% vs. 60.0%). On the other hand, a study concluded that mean INR insignificantly decreased during Ramadan compared to pre-Ramadan, despite fluctuations in INR results during Ramadan, with 66% of patients within the desired therapeutic range during Ramadan, down from 74% pre-Ramadan (12).

During Ramadan, there was an increase in out-of-range INR values, particularly in the supra-therapeutic direction, affecting

both high and low target INR groups. This amplified fluctuation on both sides of the therapeutic range likely explains the insignificant difference in overall mean INR before and during Ramadan as observed in another study of Alghamdi., et al (12). Contradictory findings were reported by Sridharan., et al (10), where fewer patients reached the therapeutic range during Ramadan, and more were within the subtherapeutic range, with a significantly higher proportion in the supra-therapeutic range post-Ramadan.

Following Ramadan, our study noted an over-correction of INR readings, with a significant decrease in mean INR, therapeutic, and supra-therapeutic INR results, accompanied by an increase in the percentage of patients with time below the therapeutic range, exceeding pre-Ramadan levels. The most significant fluctuation in achieving optimal therapeutic anticoagulation was observed between the last two weeks of Ramadan and post-Ramadan, possibly due to significant changes in dietary habits after Ramadan and increased food intake during the first week post-Ramadan. These results can be attributed to various factors, including fasting, dietary pattern changes, timing of food intake, and dehydration due to daytime fluid withdrawal. Metabolically, fasting during Ramadan has been shown to lead to temporary reductions in body weight, blood glucose, and high-density lipoprotein levels, along with increased low-density lipoprotein levels (13).

Conclusion

Ramadan fasting can lead to significant fluctuations in INR levels in patients with mechanical prosthetic heart valves using Warfarin. Careful monitoring and adjustment of anticoagulation therapy may be necessary to maintain therapeutic INR ranges during this religious observance.

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