Short Communication

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An Evaluation of the Effectiveness of Water, Milk and Natural Lemon Juice in Hepatic Biliary Secretion of ^{99m}tc-Mibi Radiopharmaceutical in Myocardial Perfusion Imaging

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ABSTRACT

BACKGROUND AND OBJECTIVE: Interfering sub-diaphragmatic activity in the liver, bile ducts and intestines is one of the complications of myocardial perfusion imaging in the diagnosis of coronary artery disease. The aim of this study was to compare the effectiveness of water, milk and natural lemon juice on liver secretion and reduction of ^{99m}Tc-sestamibi radiopharmaceutical radiation in this type of imaging.

METHODS: This clinical study was performed on 100 female patients referred to the Shahid Beheshti Hospital in Babol for myocardial perfusion imaging using SPECT method. These patients were randomly divided into 4 groups: patients receiving no drink (group 1), patients receiving 250 ml water (group 2), patients receiving 250 ml high-fat milk (group 3), and patients receiving 250 ml diluted lemon juice was (group 4). After measuring heart and liver absorption, their ratio was calculated (heart/liver). The rate of reduction of interfering sub-diaphragmatic activity after the use of these drinks in different groups was evaluated based on visual and semi-quantitative assessments.

FINDING: The four studied groups did not differ significantly in terms of age, weight, and body mass index. The H/L ratio in group 1 was 0.13±0.038, in the group 2 was 0.15±0.039, in the group 3 was 0.17±0.055 and in the group 4 was 0.15±0.039. Statistical analysis showed that interfering sub-diaphragmatic activity was only significant in group 3 in comparison with group 1 ($p=0.027$). In addition, based on visual and semi-quantitative assessments of raw data, only in group 3, 18 out of 25 patients had less interfering sub-diaphragmatic activity, which was significant compared to group 1 ($p=0.001$).

CONCLUSION: The results of the study showed that drinking at least 250 ml high-fat milk can reduce the interfering sub-diaphragmatic activity.

KEY WORDS: *Myocardial perfusion imaging, Coronary arteries, Radiopharmaceutical Technetium.*

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Introduction

Coronary Artery Disease (CAD) is a common cardiovascular disease that kills many people in modern societies, particularly at higher ages. Typically, electrocardiography (ECG) exercise testing, single-photon emission computed tomography (SPECT), and cardiac angiography are used to diagnose CAD. Myocardial perfusion imaging (MPI) is used in nuclear medicine as a non-invasive method for the diagnosis and prognosis of coronary artery disease (1, 2).

MPI is often performed in two modes of stress and rest separately, and it is possible to detect myocardial perfusion defects as well as heart failure or infarction by comparing the two scans. The stress phase occurs in two ways; pharmacological stress or exercise. Radioactive substances (radiopharmaceuticals) are used in both phases of the imaging. Currently, the most commonly radiopharmaceuticals used in this type of imaging are technetium (^{99m}Tc) derivatives such as ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin. Because of having optimum photon energy, technetium increases the contrast and provides high-quality diagnostic images (3, 4). These radiopharmaceuticals are cleansed by the liver and excreted through the extrahepatic biliary system, resulting in interfering sub-diaphragmatic radioactivity in the liver, bile ducts and intestines (5, 6).

Therefore, the appearance of this radioactivity in the sub-diaphragmatic area may produce false negative and false positive results in the studies of myocardial perfusion imaging (8, 7). Due to the proximity of the liver and the intestine to the inferior wall of myocardium, reliable judgment about CAD in this area can be difficult (9). The appearance of significant sub-diaphragmatic radioactivity is unpredictable in myocardial perfusion imaging. Therefore, sufficient hepatobiliary clearance and digestive tract clearance is necessary to obtain high quality images for interpretation (2). Reliable interpretation of heart scan can be problematic due to the disturbing radioactivity in the sub-diaphragm, especially in the liver, bile ducts and intestines. Some of the available solutions include the use of some foods and fluids to reduce or eliminate the problem by increasing the hepatobiliary and intestinal transmission of radiopharmaceuticals, which include eating high-fat foods, drinking milk, drinking milk and water, injection of cholecystokinin, and administration of metoclopramide. High-fat foods release cholecystokinin (CCK), which results in increased biliary secretion and evacuation of the gallbladder, thereby leading to increased hepatobiliary clearance and reduced interfering sub-diaphragmatic radioactivity (10-12). In the study of Hofman et al., the group that received milk had a significant reduction in sub-diaphragmatic radioactivity compared to the group that received water, but interpretation of the images was not improved (13). Furthermore, Purbhoo et al. showed that diluted lemonade and milk significantly reduced the interfering sub-diaphragmatic and hepatic radioactivity in heart perfusion imaging using ^{99m}Tc-sestamibi radiopharmaceuticals, which was more pronounced in the group receiving milk (14). In the study of Malek et al., the group that received milk had significantly lower interfering radioactivity than those receiving lemon juice and water, resulting in higher image quality (15).

Two methods are used in the stress phase: exercise (treadmill) or medication. To cause pharmaceutical stress, vasodilators such as dipyridamole or adenosine are commonly used to create coronary arterial hyperemia. Interfering splanchnic radioactivity is more prominent in pharmaceutical stress method compared to exercise method due to the effect of splanchnic vasodilation. According to available information, acidic drinks increase liver secretion and bile duct movements (13). Therefore, water, milk and diluted lemon juice were used in this study as beverages to investigate their effect on the hepatobiliary secretion of ^{99m}Tc-sestamibi radiopharmaceutical, which results in a reduction in interfering sub-diaphragmatic radioactivity.

Methods

After being approved by the ethics committee of Babol University of Medical Sciences with the code of ethics MUBABOL.REC.1394.26 and the code IRCT: 2015080123441N1, this clinical trial was conducted among 100 female patients referred to the nuclear medicine department of Shahid Beheshti Hospital in Babol for myocardial perfusion imaging using SPECT method. Patients with previous history of cholecystectomy, hepatobiliary disease, peptic ulcer, diabetes, history of myocardial infarction, heart valve disease and heart failure were included. The stress phase of heart scan is typically performed first in Shahid Beheshti Hospital in Babol. Considering the normal myocardial perfusion in stress phase, it is possible to ignore the next phase of the study (resting phase), which reduces the patient's radiation. Thus, in order for such a strategy to work, getting high-quality image in the stress phase is very important. Accordingly, this study was carried out only in the stressful step using the pharmaceutical method (prescribing dipyridamole).

Considering that most patients referred for heart scan were female, and to have patients with similar characteristics in terms of gender, age and body mass index, only female patients were selected in this study for ease of work. Patients referred for myocardial perfusion imaging using SPECT method were randomly divided to four groups in the stress phase (with drug): patients receiving no drink (group 1), patients receiving 250 ml water (group 2), patients receiving 250 ml high-fat milk (group 3), and patients receiving 250 ml diluted lemon juice (100 ml of lemon juice in 150 ml of water) (group 4). 10 minutes after receiving the radiopharmaceutical, patients received a drink depending on the group. Thirty minutes after receiving the target drink, a 2-dimensional (planar) image of the patients was captured in the anterior view for 90 seconds. Then, the absorption ratio of the heart to liver (H/L ratio) was estimated for all patients by drawing ROIs (regions of interest) on the heart and right lobe of the liver. In addition, after capturing the images, a visual and semi-quantitative assessment of sub-diaphragmatic radioactivity was done. Then, SPECT imaging was done with a SIEMENS Orbiter Nuclear Gamma Camera equipped with a low-energy, high-resolution autocollimator by routine (images were recorded over 180° around the patient in 64×64 matrices with an acquisition time of 25 seconds per projection [32 projections] with 1.2 zoom factor). Subsequently, pharmaceutical radiation in the liver, bile ducts and intestines were judged in all patients after processing the SPECT images. The visual and semi-quantitative raw data analysis was performed according to the study of Hofman et al. (13).

The presence of interfering sub-diaphragmatic radioactivity was categorized as follows: Zero: the absence of interfering sub-diaphragmatic radioactivity, One: sub-diaphragmatic radioactivity lower than diaphragmatic radioactivity, Two: sub-diaphragmatic radioactivity equal to diaphragmatic radioactivity, and Three: sub-diaphragmatic radioactivity higher than diaphragmatic radioactivity. Patient characteristics and H/L ratio are expressed as mean±standard deviation. The difference in mean H/L ratio among the groups was assessed by one-way ANOVA. The comparison between the groups was also performed by Tukey post-hoc test. Chi-square test was used to determine the effect of different drinks on interfering sub-diaphragmatic radioactivity and $p<0.05$ was considered statistically significant.

Results

The mean age in group 1 (without receiving) was 54.72±9.68, in group 2 (water) was 55.44±9.98, in group 3 (high-fat milk) was 52.24±10.78, and in group 4 (lemon juice) was 49.56±10.33 years old. The results of statistical tests showed that the variables of age (p=0.97), weight (p=0. 93) and BMI (p=0.95) did not show any significant difference between groups. The H/L ratio in group 2 was 0.15±0.039 and in group 4 was 0.15±0.039.

In comparing the mean H/L ratio in different groups, a statistically significant difference was observed (p=0.02). Consequently, the Tukey post-hoc test showed that this difference was significant between the group receiving 250 ml of high-fat milk (group 3) compared to the group without drinking (group 1) (p=0.01) (Fig 1). As shown in Figure 1, the mean H/L ratio in patients with any intervention was significantly higher than that of the group without receiving it, but this increase was statistically significant only in the group receiving high-fat milk (group 3) (p=0.01). The findings of the visual assessment of the severity of interfering sub-diaphragmatic radioactivity are shown in Table 2.

In group 1, zero (0%) patients had no interfering sub-diaphragmatic radioactivity, 3 (12%) patients had diaphragmatic radioactivity higher than interfering sub-diaphragmatic radioactivity, 14 (56%) patients had diaphragmatic radioactivity equal to interfering sub-diaphragmatic radioactivity, and 8 (32%) patients had diaphragmatic radioactivity lower than interfering sub-diaphragmatic radioactivity. These values in group 2 were 0 (0%), 4 (16%), 13 (52%) and 8 (32%), in group 3 were 4 (16%), 14 (56%), 5 (20%) and 2 (8%) and in group 4 were 2 (8%), 4 (16%), 10 (40%) and 9 (36%), respectively. The result of the chi-square test showed that there was a significant relationship between the study groups and the severity of interfering sub-diaphragmatic radioactivity (p=0.001) (Table 2). In the quantitative visual assessment, most patients in groups 1, 2 and 4 had almost equal diaphragmatic absorption and sub-diaphragmatic absorption, and only in patients in group 3, most patients had diaphragmatic absorption higher than sub-diaphragmatic absorption. Moreover, while one third of patients in groups 1, 2, and 4 had higher sub-diaphragmatic absorption, these values were significantly reduced in patients in group 3.

Table 1. Demographic characteristics of the study patients

Variable	Group 1	Group 2	Group 3	Group 4	P-value
Age (year)	54.72±9.68	55.44±9.98	52.24±10.78	49.56±10.33	0.97
Weight (kg)	74. 32±12.3	74.2±12.8	73.76±11.54	75.48±15.19	0.93
BMI(kg.m2)	30±4.68	29.05±4.61	29.74±6.41	29.49±5.5	0.95

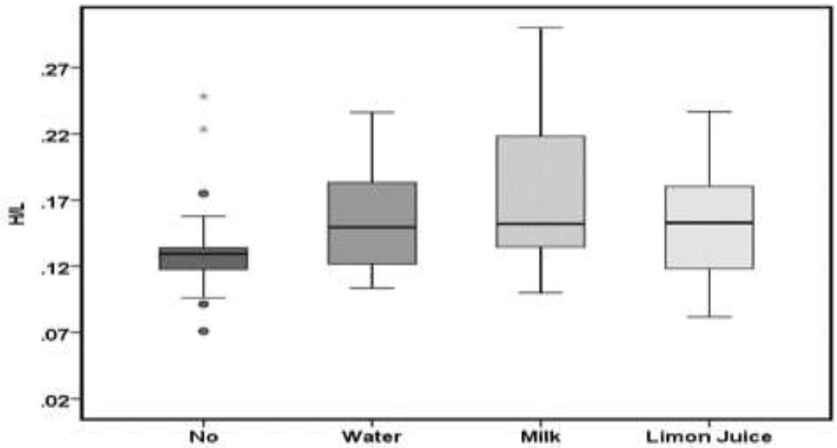

Figure 1. H/L ratio of different groups of patients

Table 2. Comparison of visual assessment of interfering sub-diaphragmatic radioactivity in different groups

Radiation Severity / Group	Lack of interfering radioactivity	Diaphragmatic absorption > sub-diaphragmatic radioactivity	Diaphragmatic absorption=sub-diaphragmatic radioactivity	Diaphragmatic absorption < sub-diaphragmatic radioactivity
Not receiving(1)	0(0)	3(12)	14(56)	8(32)
Water(2)	0(0)	14(16)	13(52)	8(32)
Milk(3)	4(16)	14(56)	5(20)	2(8)
Lemon juice(4)	2(8)	4(16)	10(40)	9(36)

P=0.001

Discussion

According to the results of this study, we can use high-fat milk to reduce interfering sub-diaphragmatic radioactivity in myocardial perfusion imaging using SPECT method, which leads to increased image quality. In some studies, milk has been used as a fatty drink for this purpose, and contradictory results have been published in this regard so far (13-17). In some other studies, lemon juice has been mentioned as drink that affects the secretion of bile by stimulating release of secretin from the intestines. Increased release of secretin improves bile secretion, while unlike CCK, it has no significant effect on evacuation of the gallbladder. Therefore, the hepatic clearance increases by ^{99m}Tc-based radiopharmaceuticals, but interfering sub-diaphragmatic radioactivity does not increase due to their low effect on evacuation of the gallbladder (14, and 17). In this study, lemon juice did not have a significant effect on the increase in hepatobiliary clearance and the decrease in interfering sub-diaphragmatic radioactivity. This finding is in contrast with a number of related studies in this area that emphasize the potential effects of lemon juice on facilitating hepatobiliary clearance accompanied by increased secretion of secretin and decreased interfering sub-diaphragmatic radioactivity (14, 17). Perhaps the reason for this difference is associated with the lack of effect of lemon juice on evacuation of the gallbladder concurrent with the increase in hepatobiliary clearance of bile, because the physiological discharge of the gallbladder may occur simultaneously with the imaging, which can lead to an increase in interfering sub-diaphragmatic radioactivity. Cherng et al. showed that water, milk and lemon juice are useful for improving the quality of heart scan, because the mean H/L ratio in water, milk and lemon juice groups was higher than that of the group that did not receive any drink. Furthermore, the group that received lemon juice had significantly lower hepatic and sub-diaphragmatic radioactivity than other groups, and consequently, the quality of SPECT images in these patients was higher (17).

However, in our study, only the patients who received milk showed an increase in mean H/L ratio, which reduced the level of interfering sub-diaphragmatic radioactivity and increased image quality. In the case of lemon juice, there was no significant increase in the mean H/L ratio compared to the water group and the non-receiving group. In another study, Hofman et al. showed that milk leads to a significant reduction in the level of interfering sub-diaphragmatic radioactivity compared to water. The mechanism of this action can be associated with increased stomach volume due to delayed gastric emptying, which is related to high-fat meals, as well as stimulation of gallbladder contraction by the milk and subsequently, the movement of radiopharmaceuticals from liver to duodenum (13).

The findings of this study can be considered similar to our study in terms of the effect of milk on reducing the interfering sub-diaphragmatic radioactivity. However, according to the study of Peace et al., drinking 150 ml of high-fat milk and 450 ml of water together did not increase the radiopharmaceutical's hepatobiliary secretion and did not decrease the interfering sub-diaphragmatic radioactivity (16). Malek et al. also reported similar results in their study. According to their study, among the groups of water and milk (125 ml of water and 125 ml of high-fat milk), lemon juice (250 ml diluted lemon juice), milk (250 ml high-fat milk), water (250 ml) and the group without drinking, only patients who received 250 ml of milk, showed a decrease in interfering sub-diaphragmatic radioactivity and an improvement in the quality of the images, 10 minutes after the injection of ^{99m}Tc sestamibi (15).

In this study, only patients who received high-fat milk had higher H/L ratio compared with other groups, and this decrease in interfering sub-diaphragmatic radioactivity increased the diagnostic power of the study, which is due to the decrease in artifacts in the images. Therefore, it can be concluded that drinking 250 ml of high-fat milk, 10 minutes after ^{99m}Tc-MIBI injection, reduces interfering sub-diaphragmatic radioactivity and improves image quality.

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