ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Influence of Low and Iso-osmolar Contrast Media on Diagnostic Performance of Contrast Fractional Flow Reserve Measurement

Düşük Ozmolar ve İzo-ozmolar Kontrast Maddenin Kontrast Fraksiyonel Akış Rezervi Ölçümünün Diagnostik Performansı Üzerindeki Etkisi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: For fractional flow reserve measurement, contrast media can be used as an alternative for adenosine. However, contrast media with different physical characteristics (e.g., osmolality and viscosity) may have different effects on hyperemia. This study aimed to determine if the diagnostic accuracy of contrast fractional flow reserve was influenced by 2 commonly used contrast media (Visipaque and Ultravist).

Methods: In this diagnostic study, candidates for coronary angiography with intermediate coronary lesion were enrolled and randomized to receive either an iso-osmolar contrast media (Visipaque) or a low osmolar contrast media (Ultravist) for fractional flow reserve measurement. The gold standard was fractional flow reserve measured by adenosine fractional flow reserve. Then cFFR and adenosine fractional flow reserve were compared between the groups, and the diagnostic values of both contrasts were calculated. Finally, the cut-point for diagnosing adenosine fractional flow reserve ≤ 0.8 was calculated for cFFR in both groups.

Results: In this study, 46 patients were studied (24 patients received Ultravist and 22 patients received Visipaque). There was no significant difference between the groups in adenosine fractional flow reserve. Also, the mean cFFR was not different from the mean adenosine fractional flow reserve in both groups. There was a strong correlation between cFFR and adenosine fractional flow reserve for each of the contrasts ($r=0.937$ for Ultravist and $r=0.927$ for Visipaque). Both contrasts had high specificity to diagnose fractional flow reserve ≤ 0.8 (specificity = 1), and the sensitivities of cFFR for Ultravist and Visipaque were 83.3% and 94.7%. The cut-point to predict adenosine fractional flow reserve ≤ 0.80 was 0.845 for Ultravist and 0.835 for Visipaque.

Conclusions: Both iso-osmolar or low osmolar contrast media have an acceptable diagnostic accuracy in measuring cFFR.

Keywords: Coronary artery disease, coronary angiography, fractional flow reserve, adenosine, contrast media

ÖZET

Amaç: Fraksiyonel akış rezervi ölçümü için, adenosine alternatif olarak kontrast madde kullanılabilir. Ancak, farklı fiziksel özelliklere (örneğin ozmolalite ve viskozite) sahip kontrast maddelerin hiperemi üzerinde farklı etkileri olabilir. Kontrast fraksiyonel akış rezervi tanısal doğruluğunun yaygın olarak kullanılan iki kontrast maddeden (Visipaque ve Ultravist) etkilenip etkilenmediğini belirlemeyi amaçladık.

Yöntemler: Bu tanısal çalışmada, orta düzeyde koroner lezyonu olan koroner anjiyografi adayları kaydedildi ve fraksiyonel akış rezervi ölçümü için izo-ozmolar kontrast madde (Visipaque) veya düşük ozmolar kontrast madde (Ultravist) verilmek üzere randomize edildi. Altın standart, adenozin ile ölçülen FFR (aFFR) idi. Daha sonra gruplar arasında cFFR ve aFFR karşılaştırıldı ve her iki kontrast maddenin tanısal değerleri hesaplandı. Son olarak, her iki grupta da cFFR için aFFR≤0.8 tanısı için kesme noktası hesaplandı.

Bulgular: Kırk altı hasta incelendi (24 hasta Ultravist ve 22 hasta Visipaque aldı). aFFR'de gruplar arasında anlamlı fark yoktu. Ayrıca, ortalama cFFR, her iki grupta da ortalama aFFR'den farklı değildi. Kontrastların her biri için cFFR ve aFFR arasında güçlü bir korelasyon vardı (Ultravist için r = 0,937 ve Visipaque için r = 0,927). Her iki kontrastın da FFR≤0,8 teşhisi için yüksek özgüllüğü (özgüllük=1) vardı ve cFFR'nin Ultravist ve Visipaque için sensitiviteleri sırasıyla %83,3 ve %94,7 idi. Adenozin FFR≤0,80'i tahmin etmek için kesme noktası, Ultravist için 0.845 ve Visipaque için 0.835 idi.

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Received: November 18, 2021
Accepted: January 31, 2022

Cite this article as: Rahmani R, Ramezani M, Shafiee A. The influence of low and Iso-osmolar contrast media on diagnostic performance of contrast fractional flow reserve measurement. *Turk Kardiyol Dern Ars* 2022;50(4):264-269.

DOI:10.5543/tkda.2022.21273

Sonuç: Hem izo-ozmolar hem de düşük ozmolar kontrast madde, cFFR'nin ölçümünde kabul edilebilir bir tanısal doğruluğa sahiptir.

Anahtar Sözcükler: Koroner arter hastalığı, koroner anjiyografi, fraksiyonel akış rezervi, adenosin, kontrast madde

Fractional flow reserve (FFR) is an accepted measure for functional assessment of coronary artery stenosis and has high sensitivity and specificity for predicting the magnitude of stenosis.[1,2] Fractional flow reserve reflects the effect of the stenosis on delaying the blood flow during the hyperemic state produced by adenosine. Fractional flow reserve has been shown to have a significant impact on the management of the patients and has resulted in a better prognosis in patients following percutaneous coronary intervention (PCI).[3,4] A study has shown that routine use of FFR can change coronary revascularization strategy classification, as initially assessed by conventional coronary angiography, in 43% of cases.[5] Additionally, FFR-guided PCI is superior to an angiographic guide and is considered the best treatment modality at the moment.[6-8] Recent data from FAME-3 trial have also shown that FFR-guided PCI is non-inferior to coronary bypass graft surgery in terms of the incidence of major adverse cardiac events.[9] Therefore, FFR measurement is becoming an inseparable procedure before revascularization, and several methods have been proposed for it.[10]

Adenosine is generally used for inducing maximal hyperemia and for measuring FFR. Adenosine induces maximal and persistent blood flow and reduces the microvascular resistance in the coronary artery.[11] However, adenosine is contraindicated in patients with asthma or chronic obstructive pulmonary disease. Also, it can lead to conductive disorders (i.e., transient atrioventricular block).

Contrast medium, conventionally used for angiography and placing the FFR guidewire, can also induce hyperemia; however, its hyperemic effect is less than adenosine or other drugs.[11,12] By the way, limited evidence shows that contrast medium can be a good substitute for adenosine for FFR measurement.[12,13] It should be noted that contrast media have various specific characteristics and differ by osmolality and viscosity. It was suggested that the viscosity of the contrast media could affect the endothelium-derived vasodilatory response of the coronary arteries and the resulting hyperemia.[14] However, current data are too scarce to set up a protocol. Therefore, this study aimed to compare the efficacy and diagnostic value of low and iso-osmolar non-ionic contrast media in the measurement of FFR in the candidates for coronary angiography and PCI at our center.

Methods

In this double-blinded, randomized–controlled trial, we enrolled consecutive patients who were candidates for coronary angiography and had intermediate coronary stenosis. The inclusion criteria were: age > 18 years; sinus heart rhythm at the time of admission; ejection fraction > 50%; intermediate coronary stenosis (40%-70%) in angiography; and consent to take part in the study. The exclusion criteria were as follows: a history of coronary artery bypass graft surgery or PCI; a history of hypersensitivity to contrast media or contrast-induced nephropathy; chronic kidney disease (creatinine >2 mg/dL); a history of hepatic failure; malignancy; collagen-vascular disease; cardiomyopathy; congestive heart failure; ostial, long, tandem, or diffuse stenosis in coronary angiography; and left ventricular hypertrophy. Written informed consent was obtained from the participants after a full description of the study. The cardiology research board and committee of the medical ethics of Imam Khomeini Hospital approved the protocol of this study (IR.TUMS.IKHC.REC.1396.3869). The study protocol conforms to the declaration of Helsinki and its updates (2013).

A thorough medical history was obtained from the patients at the time of admission, including demographic characteristics, history of diseases, and cardiovascular risk factors. The patients were randomized using a random number generator software to receive either an iso-osmolar contrast medium (Visipaque®) or a low osmolar contrast medium (Ultravist®). Visipaque®, with the generic name *iodixanol*, is a non-ionic contrast medium and has an osmolarity of 290 mOsm/kg H2O. Ultravist®, with the generic name of *iopromide*, is also a non-ionic contrast medium with an osmolarity of 77.4 mosm/kg H2O. Coronary angiography was performed in the catheterization laboratory of our center by an expert interventionist and based on the standard protocols. All procedures were done via femoral access. At first, the patient was assessed physiologically in stable condition, and the coronary pressure distal to the stenosis (Pd) and pressure of aorta (Pa) were measured to calculate Pd/Pa. Intracoronary trinitroglycerin (25-200 µg) and intravenous unfractionated heparin (100 IU/kg) were injected. After selecting the coronary artery by the guiding catheter and advancement of a 0.014 pressure wire and advancing it distal to the stenosis, Pd/Pa was measured. Then, the contrast medium (5-10 mL) was injected into the coronary artery, and the cFFR was measured by calculating Pd/Pa. After flushing the catheter with normal saline, adenosine fractional flow reserve (aFFR) was measured by injecting intracoronary adenosine (initial dose of 50 µg for the right coronary artery and 100 µg for the left coronary artery). An aFFR ≤ 0.80 was considered as the level to detect significant coronary stenosis.

Statistical Analysis

Continuous variables are shown as mean ± standard deviation, whereas categorical variables are expressed as frequency (percentage). The Kolmogorov–Smirnov test was used to test the normality of continuous data. Continuous variables were compared between the contrast media groups by Student's *t*-test, and the chi-square test was used for comparing the categorical variables. A paired *t*-test was utilized to compare cFFR with aFFR within each group and in total. We used Bland–Altman plots to assess the agreement between the cFFR and aFFR for the contrast media groups separately and in total. We used a receiver operating characteristics curve analysis to determine the cut-point for cFFR in the prediction of aFFR ≤ 0.80. Area under the curve,

ABBREVIATIONS

aFFR	Adenosine fractional flow reserve
FFR	Fractional flow reserve
Pa	Pressure of aorta
PCI	Percutaneous coronary intervention
Pd	Pressure distal to the stenosis

Table 1. Comparing the Study Characteristics Between the Ultravist and Visipaque Groups

Characteristic[a]	Total (n=46)	Visipaque® (n=24)	Ultravist® (n=22)	P[b]
Age, year	63.0 (9.3)	60.8 (8.8)	64.5 (9.7)	.187
Male sex, n (%)	32 (69.6)	18 (75.0)	14 (63.6)	.525
Smoking, n (%)	18 (39.1)	10 (41.7)	8 (36.4)	.769
Hyperlipidemia, n (%)	10 (21.7)	6 (25.0)	4 (18.2)	.725
Hypertension, n (%)	26 (56.5)	11 (45.8)	15 (68.2)	.149
Diabetes mellitus, n (%)	12 (26.1)	9 (37.5)	3 (13.6)	.096
Creatinine, mg/dL	1.2 (0.7)	1.2 (0.2)	1.3 (0.9)	.425
Hemoglobin, g/dL	14.1 (1.3)	14.4 (1.3)	13.7 (1.4)	.101
Blood glucose, mg/dL	146.5 (44.1)	157.1 (52.1)	134.8 (30.2)	.086
Ejection fraction, %	52.7 (2.9)	53.3 (3.1)	52.0 (2.5)	.138
Presentation, n (%)				.561
Unstable angina	6 (13.6)	3 (13.0)	3 (14.3)	
STEMI	1 (2.3)	0 (0)	1 (4.8)	
Stable angina	37 (84.1)	20 (87.0)	17 (81.0)	
Vessel score, n (%)				.125
Single vessel disease	24 (52.2)	9 (37.5)	15 (68.2)	
Double vessel disease	11 (23.9)	7 (29.2)	4 (18.2)	
Triple vessel disease	8 (17.4)	5 (20.8)	3 (13.6)	
Multi-vessel disease	3 (6.5)	3 (12.5)	0 (0)	
Target vessel, n (%)				.800
LAD	38 (82.6)	19 (79.2)	19 (86.4)	
LCX	3 (6.5)	2 (8.3)	1 (4.5)	
RCA	5 (10.9)	3 (12.5)	2 (9.1)	

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction
[a]Continuous variables are shown as mean (standard deviation) and categorical variables are shown as frequency (percentage); [b]$P < .05$ was considered statistically significant.

95% CI, and *P*-values were reported accordingly. For every cut-point, sensitivity and specificity were calculated and reported. The statistical analysis was performed using Statistical Package for the Social Sciences version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 13.3.3.3 (MedCalc Software, Ostend, Belgium). A *P*-value <.05 was considered statistically significant.

Results

A total of 46 patients (mean age=63 years, 69.6% were men) met our criteria and were randomized into 2 groups. A total of 24 patients received Ultravist® and 22 patients received Visipaque®. There was no significant difference between the groups regarding the baseline variables, as shown in Table 1.

Within the Ultravist group, the cFFR values were significantly higher than aFFR (0.871 ± 0.050 vs. 0.839 ± 0.063, respectively; $P < .001$). A similar difference was also observed in the Visipaque group (0.877 ± 0.045 vs. 0.843 ± 0.057, respectively; $P < .001$). In the whole study population, the cFFR values were also significantly higher than aFFR (0.874 ± 0.047 vs. 0.841 ± 0.060, respectively; $P < .001$). On the other hand, the 2 groups were not statistically different regarding aFFR and cFFR (Table 2).

cFFR had a strong linear correlation with aFFR in both groups ($r=0.937$, $P < .001$ for Ultravist and $r=0.927$, $P < .001$ for Visipaque). Also, there was a strong correlation between aFFR and cFFR for the whole study population ($r=0.922$, $P=.001$). We also observed a good agreement with minimal scatter of data in the Bland–Altman analysis between aFFR and cFFR for both groups (Figure 1).

The cutpoint of cFFR for predicting aFFR ≤ 0.8 was 0.845 for Ultravist (sensitivity=94.7% and specificity=100%) and 0.835 for Visipaque (sensitivity=83.3% and specificity=100%) (Table 3).

Discussion

This study showed that contrast media could be used safely and effectively for FFR measurement, and both Ultravist and Visipaque were able to provide sufficient hyperemia to measure FFR. On the other hand, there was no significant difference between the FFRs measured by low and iso-osmolar contrast media. Calculated cut-points for cFFR can predict aFFR with high sensitivity and specificity. Higher cut-points than aFFR may result from lower hyperemia induced by contrast media compared to adenosine.

Fractional flow reserve is a practical tool for measuring the severity of coronary stenosis, and its advantage is its availability and possibility of performance in the catheterization laboratory.[15] Fractional flow reserve is the gold standard for hemodynamic evaluation of the intermediate lesions of the

Table 2. Comparing aFFR Measurements and cFFR Between the Study Groups

Characteristic[a]	Visipaque® (n=24)	Ultravist® (n=22)	P[b]
Total adenosine dose, mcg	570.8 (142.8)	665.9 (218.9)	.086
Adenosine FFR	84.3 (6.4)	84.3 (5.7)	.987
Contrast FFR	87.1 (5.1)	87.7 (4.5)	.673
Pd/Pa	91.9 (5.1)	93.1 (4.0)	.391
FFR difference[‡]	2.8 (2.7)	3.4 (2.5)	.673

FFR, fractional flow reserve; Pd, coronary pressure distal to the stenosis; Pa, pressure to aorta.
[a]Continuous variables are shown as mean (standard deviation);
[b]$P < .05$ was considered statistically significant.

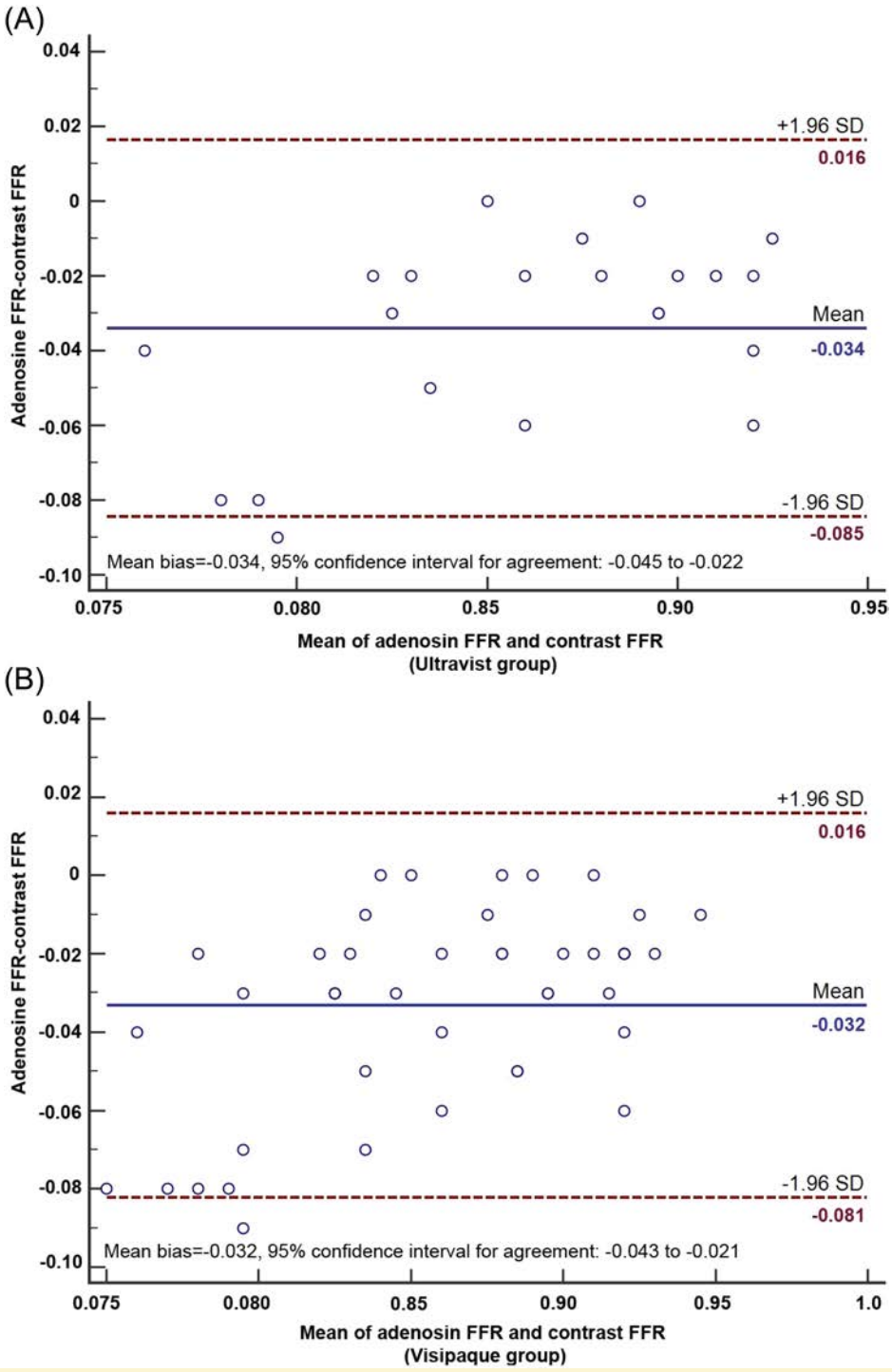

Figure 1. Bland–Altman plots showing agreement between adenosine FFR and contrast FFR in the Ultravist group (A) and Visipaque group (B). FFR, fractional flow reserve.

Table 3. Cut-Points of Contrast Media FFR for Predicting Adenosine FFR ≤ 80%

Contrast	Cut-Point Level	Sensitivity	Specificity	AUC	95% CI	*P**
Visipaque®	0.835	0.947	1	0.979	0.928-1.000	.001
Ultravist®	0.845	0.833	1	0.965	0.892-1.000	.004

AUC, area under the curve.
*$P < .05$ was considered statistically significant.

coronary artery.[16-19] Therefore, a combination of diagnostic angiography and FFR provides a unique opportunity to gain anatomic and functional information of coronary arteries simultaneously. The average time for obtaining FFR at the end of a diagnostic coronary angiography is 7 minutes for a single coronary artery and 15 minutes for 2 or more vessels.[20] This duration is much shorter than the time needed for performing laborious tests, such as stress echocardiography, myocardial perfusion scan, or any other functional cardiac imaging. Evidence shows that the long-term risk for the incidence of major adverse cardiac events following FFR-based PCI is significantly lower than the angiography-based PCI.

During FFR measurement, maximal hyperemia should be induced by adenosine.[11,21,22] However, due to the challenges with adenosine, the use of other compounds for FFR measurement has attracted attention. It has been known for a long time that the contrast medium has hyperemic properties.[23] The mechanism of contrast-induced hyperemia is not well defined; however, it seems that it happens by transient hypoxia from the replacement of oxygenated blood and stimulation of endothelial paracrine pathways.[24] Accordingly, studies have shown that contrast-induced hyperemia is high enough to assess the intermediate coronary stenosis, and it can be used effectively for FFR measurement.[23,25] Measurement of FFR with 8 different contrast media in 763 subjects showed that contrast media has a good diagnostic performance in measuring FFR (diagnostic accuracy=85.8%).[26] However, the author did not perform a sub-analysis to see whether the type of contrast media influences the diagnostic features. Leone et al[12] studied 80 patients with 104 intermediate coronary lesions and showed cFFR at a cut-point of ≤0.83 could predict aFFR value ≤0.80 with a sensitivity of 85.7 and a specificity of 96.1. They used iomeprol, which is a low osmolar contrast medium. In one study, there was a strong relationship and agreement between cFFR and aFFR in 102 intermediate coronary lesions (r=0.94, 95% CI of disagreement: −0.029 to 0.072), and cFFR could predict FFR< 0.80 at a cut-point of 0.83, which is very similar to our findings. Kanaji et al[27] used a non-ionic low-osmolar contrast medium (iomeprol) to measure FFR in 91 intermediate stenoses and found that cFFR has a high correlation with conventional FFR and could diagnose aFFR ≤ 0.80 with a diagnostic accuracy of 81.2%.

Similarly, Spagnoli et al[28] studied cFFR with iodixanol in 138 coronary lesions and found that cFFR has excellent accuracy in predicting FFR < 0.80 at a cut-point of 0.085 that is again comparable to our cut-point level. There was a strong correlation between cFFR and aFFR in Topcu et al[13] study (0.886), as well as a good agreement (mean bias=0.027). A cFFR of 0.85 could also predict aFFR < 0.80 with a sensitivity of 90.9 and specificity of 91.7%, which is similar to our findings. In a very comparable study, low and iso-osmolar contrasts were compared for their diagnostic value for FFR measurement, and the results showed that the measured FFR was not significantly influenced by contrast volume and osmolality.[29] However, this was not a randomized study, and our results can be an excellent complement to the previous findings. Applicability of contrast utilization is of value and it has been shown that its diagnostic performance does not differ between sexes.[30]

The unique finding of this study is that we did not observe any difference between 2 physically different contrast media in the measurement of FFR, and both could predict aFFR ≤ 0.80 with high sensitivity and specificity at the calculated cut-point levels. Therefore, our evidence adds to the current knowledge that contrast media can be used for FFR measurement, and its osmolality does not significantly affect this measurement.

Limitations

The main limitation of this study is its small sample size. Therefore, the cut-off levels determined in this study need to be confirmed in larger studies.

Conclusion

Our study showed that both low and iso-osmolar contrast media could be used effectively to measure FFR during PCI, and there was no significant difference between them in this measurement. However, we recommend more extensive clinical trials using various types of contrast media to elucidate the exact effect of contrast medium on FFR measurement.

Ethics Committee Approval: Ethics committee approval was received for this study from the Imam Khomeini Hospital (Approval Number: IR.TUMS.IKHC.REC.1396.3869).

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.R.; Design - R.R.; Supervision - R.R.; Data Collection and/or Processing - M.R.; Analysis and/or Interpretation - A.S.; Literature Review - R.R., M.R., A.S.; Writing - R.R., M.R., A.S.; Critical Review - A.S.

Declaration of Interests: None of the authors have conflicts of interest to declare.

Funding: This study was supported by the Tehran University of Medical Sciences, Tehran, Iran (Grant Number: 9411171026).

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