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Comparison of Regadenoson and Dipyridamole Safety Profiles During Stress Myocardial Perfusion Imaging

Stres Miyokardiyal Perfüzyon Görüntüleme Esnasında Regadenozon ve Dipiridamol Güvenlik Profillerinin Karşılaştırılması

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Abstract

Objectives: The pharmacological stress test with vasodilator agents is an alternative cardiological diagnostic tool for patients with contraindications to the classical stress test provided by physical activity during single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). The study compared the frequency of the side effects of regadenoson and dipyridamole during a SPECT MPI.

Methods: This retrospective study included data of 283 consecutive patients who underwent pharmacological stress tests in years 2015-2020. The study group consisted of 240 patients who had received dipyridamole and 43 patients who had received regadenoson. The collected data included the patients' characteristics, the occurrence of side effects (divided into mild: headache, vertigo, nausea, vomiting, dyspnea, chest discomfort, hot flushes, general weakness and severe: bradycardia, hypotension, loss of consciousness), and blood pressure values/measurements.

Results: Overall, complications occurred relatively often (regadenoson: 23.2%, dipirydamol: 26.7%, p=0.639). Procedure discontinuation was necessary in 0.7% of examinations, whereas pharmacological support was necessary in 4.7%. There was no difference in the prevalence of mild (regadenoson: 16.2%, dipirydamol: 18.3%, p=0.747) and severe complications (regadenoson: 11.6%, dipyridamole: 15.0%, p=0.563). However, regadenoson has been found to cause a significantly smaller mean decrease of systolic blood pressure (SBP) (regadenoson: -2.6±10.0 mmHg, dipyridamole: -8.7±9.6 mmHg, p=0.002), diastolic blood pressure (DBP) (regadenoson: -0.9±5.4 mmHg, dipyridamole: -3.6±6.2 mmHg, p=0.032), as well as mean arterial pressure (MAP) (regadenoson: -1.5±5.6 mmHg, dipyridamole: -5.4±6.5 mmHg, p=0.001).

Conclusion: Regadenoson and dipyridamole presented a similar safety profile during SPECT MPI. However, regadenoson has been found to cause significantly smaller decreases in SBP, DBP, and MAP.

Keywords: Regadenoson, dipyridamole, myocardial perfusion imaging, vasodilators, stress test, single photon emission computed tomography

Öz

Amaç: Vazodilatör ajanlarla yapılan farmakolojik stres testi, tek foton emisyonlu bilgisayarlı tomografi (SPECT) miyokardiyal perfüzyon görüntülemesi (MPI) sırasında fiziksel aktivite ile sağlanan klasik stres testinin uygulanmasının kontrendike olduğu hastalar için alternatif bir kardiyolojik tanı aracıdır. Bu çalışmada, SPECT MPI sırasında regadenozon ve dipiridamolün yan etkilerinin sıklığı karşılaştırıldı.

Yöntem: Bu retrospektif çalışma, 2015-2020 yıllarında farmakolojik stres testi uygulanan ardışık 283 hastanın verilerini içermektedir. Dipiridamol alan 240 hasta ve regadenozon alan 43 hasta çalışma grubunu oluşturdu. Toplanan veriler içinde hastaların özellikleri, ortaya çıkan yan etkiler (baş

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ağrısı, vertigo, mide bulantısı, kusma, nefes darlığı, göğüs rahatsızlığı, sıcak basması ve genel halsizlik hafif yan etkiler; bradikardi, hipotansiyon ve bilinç kaybı şiddetli yan etkiler olarak sınıflandırıldı) ve kan basıncı değerleri/ölçümleri bulunmaktaydı.

Bulgular: Genel olarak, komplikasyonlar nispeten sık meydana geldi (regadenozon: %23,2, dipiridamol: %26,7, p=0,639). Muayenelerin %0,7'sinde işlem sona erdirilirken, %4,7'sinde farmakolojik destek gerekliydi. Hafif (regadenozon: %16,2, dipiridamol: %18,3, p=0,747) ve ağır komplikasyonların (regadenozon: %11,6, dipiridamol: %15,0, p=0,563) prevalansları açısından fark yoktu. Bununla birlikte, regadenozonun sistolik kan basıncında (SBP) (regadenozon: -2,6±10,0 mmHg, dipiridamol: -8,7±9,6 mmHg, p=0,002), diyastolik kan basıncında (DBP) (regadenozon: -0,9±5,4 mmHg, dipiridamol: -3,6±6,2 mmHg, p=0,032) ve ortalama arter basıncında (MAP) (regadenozon: -1,5±5,6 mmHg, dipiridamol: -5,4±6,5 mmHg, p=0,001) anlamlı olarak daha az düşüş ile ilişkili bulunmuştur.

Sonuç: Regadenozon ve dipiridamol, SPECT miyokard perfüzyon görüntülemesi sırasında benzer bir güvenlik profili sergilemiştir. Bununla birlikte, regadenozonun SBP'de, DBP'de ve MAP'de anlamlı olarak daha az düşüşe neden olduğu bulunmuştur.

Anahtar kelimeler: Regadenozon, dipiridamol, miyokardiyal perfüzyon görüntüleme, vazodilatörler, stres testi, tek foton emisyonlu bilgisayarlı tomografi

Introduction

Coronary artery disease (CAD) is a cardiovascular condition that involves atherosclerotic plaque formation in the vessel lumen. Due to impairment in the blood flow, oxygen delivery to the myocardium is disturbed (1). For this reason, CAD is proved to be one of the main causes of death in developed and developing countries and should be properly diagnosed and treated (2). The single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is a non-invasive diagnostic tool that is performed in patients with suspected CAD. This method is a superior alternative to the treadmill electrocardiography test, especially in patients with single-vessel CAD, with superior safety profile compared to the invasive diagnostic procedure, namely coronary arteriography (3,4). This imaging technique shows myocardial perfusion and the effects of stress on the heart muscle. SPECT MPI is a nuclear medicine imaging technique using gamma rays and radiopharmaceuticals such as Technetium-99m; it may be performed in a one- or two-day protocol (5). In the one-day protocol, the patient undergoes a rest SPECT scan in the morning and then a SPECT stress scan after 4 h. In the 2-day protocol, only one SPECT scan is taken daily. There are two strategies for stress testing. The most common is exercise on a treadmill with constant heart rate, blood pressure, and electrocardiographic monitoring. The second technique is pharmacological and is used if the exercise test is contraindicated (6). During this method, the patient receives one of the coronary vasodilators adenosine agonists: adenosine, regadenosine, or dipyridamole. Dipyridamole is an indirect adenosine agonist, and regadenosine and adenosine are direct agonists. Regadenoson is a selective α(2A) receptor agonist, whereas dipyridamole and adenosine can activate adenosine α(1), α(2A), α(2B) and α(3) receptors. These substances mimic physical exercise on the heart muscle (5). Each of the drugs applied to simulate cardiovascular stress causes various adverse effects due to stimulation of adenosine receptors, most commonly: headache, chest pain, decrease in blood pressure, nausea (5). Therefore, it is important to compare the most commonly used vasodilators in terms of their safety profiles. The study compared regadenoson and dipyridamole in terms of complications and impact on blood pressure during SPECT examination.

Materials and Methods

The study included 283 consecutive patients who underwent pharmacological stress SPECT in years 2015-2020 in the John Paul II Hospital in Kraków, Poland. The study population consisted of two groups: 240 patients who had received dipyridamole (Persantin, Boehringer Ingelheim Pharmaceuticals Inc, Germany) and 43 patients who had received regadenoson (Rapiscan, GE Healthcare AS, Norway). The inclusion criteria were having undergone a pharmacological stress SPECT with the administration of dipyridamole or regadenoson and age above 18 years. Each patient included in the study gave informed consent to perform pharmacological stress SPECT. The exclusion criteria were the contraindications to the pharmacological stress with vasodilators (a history of severe bronchospasm, asthma during physical activity, severe aortic stenosis, severe obstructive hypertrophic cardiomyopathy, pregnancy or lactation, 2° or 3° degree, atrioventricular block and atrial node disease, arterial hypotension (SP <90 mmHg), or history of allergic reaction to the previously mentioned drugs) (7). The collected data included the characteristics of the patients such as sex, age, body mass index (BMI), medical information regarding chronic diseases like diabetes, hypertension, atherosclerosis, hyperlipidemia as well as past myocardial infarction (MI) or heart failure and the history of medical procedures [percutaneous coronary interventions (PCI), and coronary artery bypass graft surgery (CABG)] as well as information regarding to the stress MPI procedure: side effects (divided into mild: headache,

vertigo, nausea, vomiting, dyspnea, chest discomfort, hot flushes, overall weakness, and severe: bradycardia (defined as heart rate below 60), hypotension [defined as systolic blood pressure (SBP), <90 or mean blood pressure (MBP) <70 and loss of consciousness] and blood pressure measurements: before the procedure, 5 times during the procedure (every minute) and 4 times after the procedure (every minute). Standard descriptive statistics were used to describe the data. Categorical variables were presented as percentages. Quantitative data were presented as mean value ± 1 standard deviation for data with normal distribution or median with interquartile range quartile 1 and 3, respectively for data with distribution other than normal.

Statistical Analysis

The normality of the data was assessed using the Shapiro-Wilk test for samples smaller than 50 or Kolmogorov-Smirnov test for samples greater than 50. Quantitative variables with a normal distributions were compared using the Student's t-test. Non-normally distributed quantitative variables were compared using Mann-Whitney Wilcoxon U test. Categorical variables were compared using Pearson's chi-square test. The statistical significance was set at $p \leq 0.05$. All analyses were carried out with the software TIBCO Software Inc. (2017). Statistical (data analysis software system) version 13. http://statistica.io.

The study was provided with the ethical principles for clinical research based on the Declaration of Helsinki. Every patient included in the study gave informed consent for the SPECT examination. The Bioethics Committee of Jagiellonian University approved this study (approval no: 1072.6120.155.2021). It gave consent to the use of patient health data related directly to the perfusion SPECT (the course of the procedure, complications, the measure given) as well as general information containing demographic data and information on general health for conducting the study. The bioethics committee waived the obligation to obtain informed consent from enrolled patients due to the retrospective nature of the study.

Results

The study group consisted of 283 patients who underwent pharmacological stress tests, 240 of whom had been administered dipyridamole and 43 regadenoson. The most common chronic condition was hypertension, followed by hyperlipidemia, atherosclerosis, and obesity. Both groups were comparable in terms of chronic diseases, BMI, past cardiovascular history MI, PCI, and CABG. The full characteristics of patients are presented in the table below (Table 1).

Overall, complications occurred relatively often (regadenoson: in 10 of 43;23.2%, dipyridamole: in 64 of 240; 26.7%, p=0.639). The majority was mild complications (regadenoson: in 7 of 43; 16.2%, dipyridamole: in 44 of 240; 18.3%, p=0.747); however, therewas also a high occurrence of severe complications (regadenoson: in 5 of 43; 11.6%, dipyridamole: in 36 of 240; 15.0%, p=0.563). The difference between the two vasodilator drugs in terms of specific and pooled complications was not significant. A detailed comparison has been presented in Table 2.

The differences in MBP values SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) during and

Table 1. Characteristics of the study group

	Total	Regadenoson (n=43)	Dipirydamol (n=240)	p value
Age (years)	70.4±9.2	71.0±7.4	70.3±9.5	0.638
Male sex	158 (55.8%)	24 (55.8%)	134 (55.8%)	0.993
BMI (kg/m^2)	29.7±5.15	30.3±6.9	29.8±4.6	0.892
Obesity (BMI >30)	123 (43.5%)	17 (39.5%)	106 (44.2%)	0.639
Diabetes mellitus type 2	87 (30.9%)	10 (23.3%)	77 (32.2%)	0.241
Hypertension	227 (80.5%)	30 (69.8%)	197 (82.4%)	0.054
Atherosclerosis	139 (49.3%)	20 (46.5%)	119 (49.8%)	0.692
Hyperlipidemia	197 (69.5%)	31 (72.1%)	166 (69.5%)	0.729
Past MI	86 (30.5%)	11 (25.6%)	75 (31.4%)	0.447
Past PCI	89 (31.6%)	12 (27.9%)	77 (32.2%)	0.576
Past CABG	28 (9.93%)	4 (9.3%)	24 (10.0%)	0.881
Heart failure	118 (41.8%)	15 (34.9%)	103 (43.1%)	0.315

Quantitative data with normal distribution has been presented as mean ± standard deviation. Categorical variables have been presented as counts with percentages in brackets. BMI: Body mass index, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting

Table 2. Detailed comparison of complications				
	Total	**Regadenoson (n=43)**	**Dipyridamole (n=240)**	**p value**
Complications	74 (26.1%)	10 (23.2%)	64 (26.7%)	0.639
Mild complications	51 (18.0%)	7 (16.2%)	44 (18.3%)	0.747
-Headache	15 (5.3%)	0	15 (6.25%)	0.092
-Vertigo	4 (1.4%)	1 (2.3%)	3 (1.3%)	0.582
-Nausea	1 (0.4%)	0	1 (0.4%)	0.672
-Vomiting	0	0	0	1.0
-Dyspnea	14 (4.9%)	3 (7.0%)	11 (4.6%)	0.505
-Chest discomfort	8 (2.8%)	0	8 (3.3%)	0.224
-Hot flushes	5 (1.8%)	0	5 (2.1%)	0.340
-Overall weakness	9 (3.1%)	2 (4.6%)	7 (2.9%)	0.551
Severe complications	41 (14.4%)	5 (11.6%)	36 (15.0%)	0.563
-Bradycardia	6 (2.1%)	2 (4.7%)	4 (1.7%)	0.211
-Hypotension	38 (13.4%)	5 (11.6%)	33 (13.75%)	0.707
-Loss of consciousness	0	0	0	1
Procedure discontinuation	2 (0.7%)	0	2 (0.8%)	0.548
Aminophylline administration	14 (4.9%)	2 (4.7%)	12 (5.0%)	0.922
Oxygen administration	5 (1.8%)	2 (4.7%)	3 (1.3%)	0.119
Categorical variables have been presented as counts with percentages in brackets				

before the procedure are presented in Table 3. Changes in SBP, DBP and MAP values in time compared between dipyridamole and regadenoson have been presented in Figure 1. Regadenoson has been found to cause a significantly smaller mean decrease of SBP (regadenoson: -2.6±10.0 mmHg, dipyridamole: -8.7±9.6 mmHg, p=0.002) and DBP (regadenoson: -0.9±5.4 mmHg, dipyridamole: -3.6±6.2 mmHg, p=0.032), as well as MAP (regadenoson: -1.5±5.6 mmHg, dipyridamole: -5.4±6.5 mmHg, p=0.001) compared with the value before the procedure (Table 3) (Figure 2A, B, C).

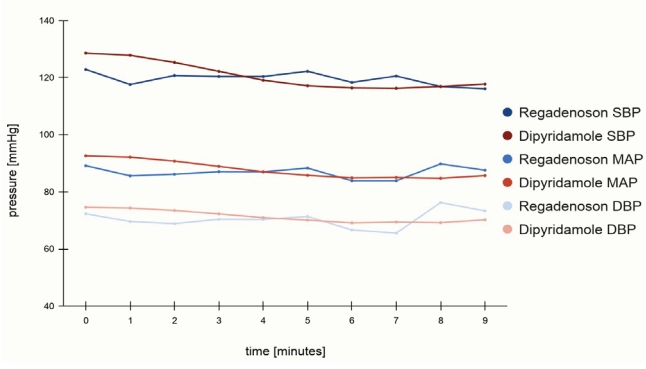

Figure 1. Change of blood pressure values in time (mmHg)
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Discussion

In this study of the vasodilators' safety profile during MPI, the administration of dipyridamole was associated with a significant decrease in systolic (8.7±9.6 mmHg versus 2.6±10 mmHg, p=0.002), diastolic (3.6±6.2 mmHg versus 0.9±5.4 mmHg, p=0.032) and MAP (5.4±6.5 mmHg versus 1.5±5.6 mmHg, p=0.001), in comparison to regadenoson. No such differences between the vasodilators were observed in terms of the symptoms reported by patients undergoing the procedure and the need for oxygen or aminophylline administration. The occurrence of any side effects was observed in 10 of 43 patients (23.2%) in regadenoson and 64 of 240 patients (26.7%) in the dipyridamole group (p=0.639). The main adverse effects of vasodilator administration were: hypotension (reported by 38 of 283 patients, 13.4%, p=0.707), headache (15 of 283, 5.3%, p=0.092), and dyspnea (14 of 283, 4.9%, p=0.505). Presented data may suggest that regadenoson is safer than dipyridamole.

In the study conducted by Amer et al. (8), regadenoson was associated with more frequent adverse effects (241 of 284, 84.9%) than dipyridamole (161 of 284, 56.7%) in patients undergoing MPI, with a p value <0.0001. There were particular types of complaints, which were statistically rarely observed in the dipyridamole group compared to regadenoson, which were: dyspnea (2.1% vs. 52.5%,

Table 3. Average change of blood pressure values during the procedure				
	Total	**Regadenoson (n=27)**	**Dipyridamole (n=240)**	**p value**
SBP change (mmHg)	**-8.1±9.8**	**-2.6±10.0**	**-8.7±9.6**	**0.002**
SBP change (% of initial value)	**-5.6 (-9.5)-(-1.0)**	**0 (-7.6)-(6.0)**	**-6.0 (-9.7)-(-1.7)**	**0.002**
DBP change (mmHg)	**-1.1 (-6.6)-(0.0)**	**0 (-4.0)-(0.0)**	**-1.1 (-7.8)-(0.0)**	**0.032**
DBP change (% of initial value)	-1.4 (-9.3)-(0.0)	0 (-5.0)-(0.0)	-1.6 (-9.7)-(0.0)	0.051
MAP change (mmHg)	**-4.0 (-8.1)-(-0.6)**	**-1.0 (-4.0)-(2.0)**	**-4.1 (-8.6)-(-1.2)**	**0.001**
MAP change (% of initial value)	**-4.1 (-8.73)-(-0.6)**	**-1.0 (-5.0)-(2.8)**	**-4.3 (-8.8)-(-1.2)**	**0.002**

Quantitative variables which followed normal distribution have been presented as mean ± standard deviation. Results with significant p values have been presented in **bold**.
Positive value = increase, negative value = decrease
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

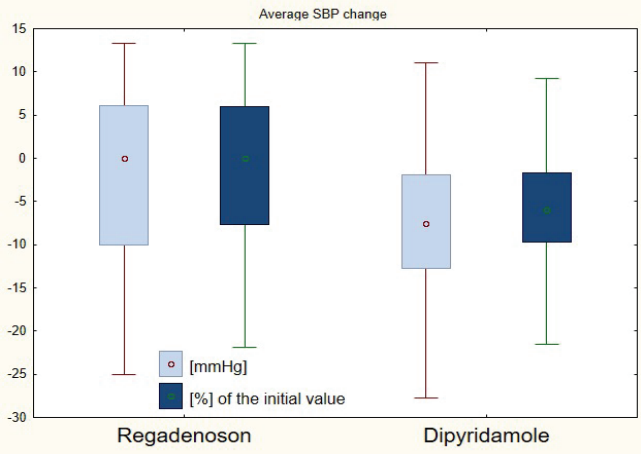

Figure 2A. Average SBP change during and after the procedure. Data has been presented as median, quartiles and non-outlier range
SBP: Systolic blood pressure

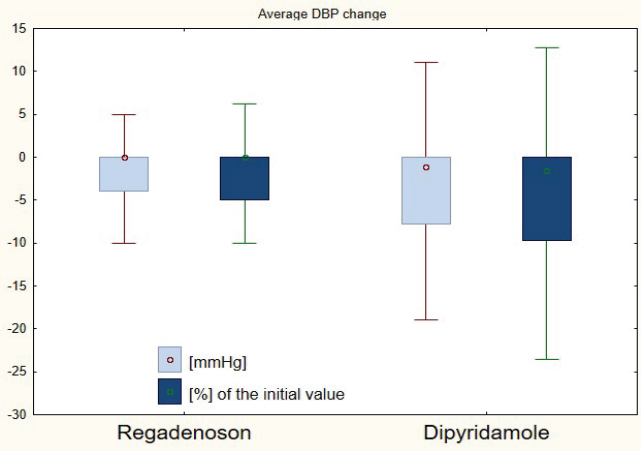

Figure 2B. Average DBP change during and after the procedure. Data has been presented as median, quartiles and non-outlier range
DBP: Diastolic blood pressure

p<0.0001), gastrointestinal discomfort (8.1% vs. 27.8%, p<0.0001) and chest pain (3.9 vs. 15.8%, p<0.0001). Hypotension was very rare: 1.1% in the regadenoson group

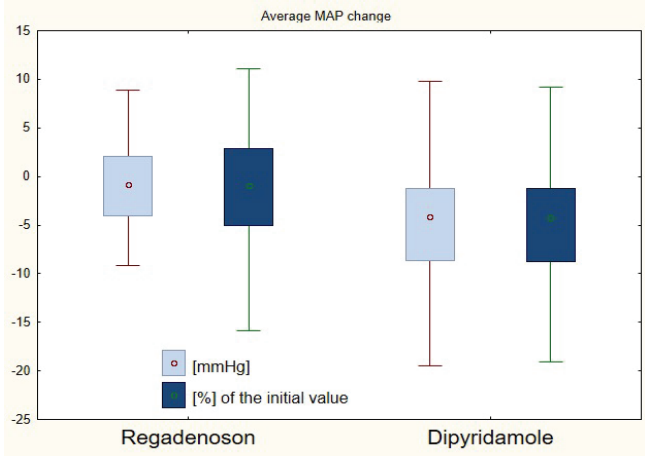

Figure 2C. Average MAP change during and after the procedure. Data has been presented as median, quartiles and non-outlier range
MAP: Mean arterial pressure

and 0% in the dipyridamole group (8). In our study, there was no statistically significant difference in dyspnea in the dipyridamole group compared with regadenoson (4.6% vs. 7%, p=0.505). Hypotension was the most common complication in both the dipyridamole and regadenoson groups. Overall, complications were rarely observed in our study than in the study by Amer et al. (8).

Goudarzi et al. (9) investigated the hemodynamic responses to regadenoson and dipyridamole. The increase in the heart rate was significantly higher in the regadenoson group than in patients who received dipyridamole (34±14 vs. 23±10 beats per minute increase from baseline; p<0.01). Stress myocardial body flow and myocardial flow reserve were not different between the groups (2.2±0.6 vs. 2.1±0.6 mL/min/g, p=0.39, and 2.9±0.8 vs. 2.8±0.7, p=0.31, respectively). If we consider the most common side effects of regadenoson, in a study conducted by Katsikis et al. (10), in the group of patients who underwent the MPI stress test, 197 of 279 women (71%) and 162 of 279 men (58%) experienced side effects of regadenoson. The following side effects occurred more frequently in women: chest

pain (65 of 279, 23% versus 33 of 279, 12%, p=<0.001), gastrointestinal discomfort (55 of 279, 20% versus 33 of 279, 12%, p=0.01) dizziness (35 of 279, 12% versus 14 of 279, 5%, p=0.002) and headache (56 of 279, 20% versus 37 of 279, 13%, p=0.03) respectively in women and men. Other adverse effects appear to be unrelated to gender (10) In another study, the most common side effects of regadenoson were: dyspnea (149 of 232 patients, 64%), headache (45 of 232, 19%), and chest pain (39 of 232, 17%). Three patients (1.3%) required administration of pharmaceuticals or hemodynamic support to relieve their symptoms. If hemodynamic responses are considered, a significant (p<0.0001) drop in SBP and DBP was observed as well as an increase in the heart rate (11). Complications of regadenoson in our study were observed more rarely compared to those studies; dyspnea was present in 7% of patients, followed by overall weakness (4.6%), and no cases of headache and chest discomfort were reported. Hypotension occurred in 11.6% and bradycardia in 4.7% of patients administered regadenoson. On the other hand, additional support was more often necessary; 4.7% of participants required administration of aminophylline and 4.7%-oxygen.

Considering the relative potency of vasodilators, regadenoson produces higher stress myocardial blood flow (95±11 vs. 86±12 beats/minute) and myocardial perfusion reserve (3.11±0.63 vs. 2.61±0.57) than dipyridamole and, if adjusted to the heart rate, has a much higher heart rate response. This means that regadenoson has superior vasodilator efficacy to dipyridamole; therefore, it could be a better agent to perform the stress MPI test (12). In a survey-based study by Friedman et al. (13), regadenoson and dipyridamole were compared in terms of duration of MPI test (156 vs. 191 min, respectively) and time from the administration to the start of the imaging procedure, including the dose calculation and infusion time, which were also shorter for regadenoson (mean difference: 12 min). Also, the time to manage the occurring adverse events was shorter in regadenoson (13).

It is worth adding that in the literature there is a certain trend in the popularity of using various vasodilators. In a survey study from 2013, the responders group consisted of the employees of healthcare facilities that perform MPI stress studies on the territory of the United States of America. In 93 of 141 (69%) imaging laboratories that took part in the survey, only one agent had been used: 38 (28%) adenosine, 27 (20%) dipyridamole, and 28 (21%) regadenoson. From 141 labs, 36 (27%) used two agents: 21 (16%) adenosine and regadenoson, 8 (6%) adenosine and dipyridamole, and 7 (5%) dipyridamole and regadenoson. Only 6 (4%) labs used all three agents (13). In a similar study from 2020, 35 of 50 (70%) participating labs were using only regadenoson, and dipyridamole or adenosine were both used in only 3 (6%) of responders' places of work. There were 10 labs (20%) using two agents, one of which was regadenoson. In 7 (14%), the other one was dipyridamole and in 3 (6%), it was adenosine. Only 2 (4%) centers used all three agents (14).

Study Limitations

This is a retrospective observational study with all its inherent biases. There was a difference in the size of the groups in this study, which could have impacted the results of statistical analysis. The duration of the symptoms was not taken into consideration because it was not available in the documentation.

Conclusion

Overall, based on our findings, regadenoson, and dipyridamole presented a similar safety profile during a SPECT MPI. There was no significant difference in the assessed complications. The occurrence of complications was high overall: 26.1%, mild: 18.0%, severe: 14.4%. Procedure discontinuation was necessary in 0.7% of examinations, whereas pharmacological support was necessary in 4.7%. However, regadenoson has been found to cause a significantly smaller decrease in SBP, DBP, and MAP, so it might be preferred for patients with lower blood pressure or a known tendency for hypotony.

Ethics

Ethics Committee Approval: The study was provided with the ethical principles for clinical research based on the Declaration of Helsinki. Every patient included in the study gave informed consent for the SPECT examination. The Bioethics Committee of Jagiellonian University approved this study (approval no: 1072.6120.155.2021).

Informed Consent: Each patient included in the study gave informed consent to perform pharmacological stress SPECT.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S., M.K., K.H., Concept: J.R., J.B., G.K., W.Z., J.O., B.C., A.S., M.K., K.H., Design: J.R., J.B., G.K., W.Z., J.O., B.C., A.S., M.K., K.H., Data Collection or Processing: J.R., J.B., G.K., W.Z., J.O., B.C., Analysis or

Interpretation: J.R., J.B., G.K., W.Z., J.O., B.C., A.S., M.K., Literature Search: J.R., J.B., G.K., W.Z., J.O., B.C., Writing: J.R., J.B., G.K., W.Z., J.O., B.C., A.S., M.K., K.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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