THE ATLANTIC Journal of Medical Science and Research

Atlantic J Med Sci Res 2023;3(4):152-6
DOI: 10.5455/atjmed.2023.05.037

Original Article

The effect of ıron deficiency and goiter on the adaptation process of iatrogenic cerebral vasodilation and cardiac parameters

Sule Ceylan

University of Health Sciences, Gaziosmanpasa Training an Research Hospital, Department of Nuclear Medicine, İstanbul, Türkiye

Received: 29 May, 2023
Accepted: 17 October, 2023
Published: 20 October, 2023

Corresponding Author: Sule Ceylan, University of Health Sciences, Gaziosmanpasa Training an Research Hospital, Department of Nuclear Medicine, İstanbul, Türkiye
Email: suleceylan2003@yahoo.com

CITATION
Ceylan S. The effect of ıron deficiency and goiter on the adaptation process of iatrogenic cerebral vasodilation and cardiac parameters. Atlantic J Med Sci Res. 2023;3(4):152-6. DOI: 10.5455/atjmed.2023.05.037

Abstract

Aim: Adenosine is a pharmacological stress agent used in many nuclear medicine clinics. It causes different and widespread effects in different tissues. It causes widespread inhibition and cerebral vasodilation through A1 and A2a receptors in the central nervous system. We evaluated the duration of side effects in patients with iron deficiency and euthyroid goiter.

Materials and Methods: Our study included 183 patients with atypical chest pain who underwent myocardial perfusion scintigraphy to investigate the presence of coronary artery disease. Adenosine infusion was administered intravenously at a rate of 140 µg/kg/min for 6 minutes. Complaints that occurred during intravenous administration of adenosine were questioned. The presence of at least three of the most common complaints of flushing, headache, nausea, and feeling of ill feeling was considered to have prominent complaints. If these complaints continued for at least 30 minutes, the presence of prolonged prominent complaints was accepted. Patients who developed prolonged complaints were categorized as group 1 and patients without prolonged complaints as group 2.

Results: The number of patients diagnosed with euthyroid goiter was significantly higher in Group 1 ($p<0.005$). Additionally, thyroid size was significantly larger in patients in Group 1 compared to those in Group 2, with respective medians (minimum-maximum) of 20 (11-18 ml) and 15 (11-28 ml) ($p<0.005$). In group 1, 44 (86.3%) patients had iron deficiency, while in group 2 37 (28%) patients had iron deficiency ($p<0.005$). The free variables determining the development of prolonged prominent complaints in patients who received adenosine infusion were found to be goiter size (Odds: 1.437, confidence interval: 1.264-1.633; $p<0.005$) and presence of iron deficiency (Odds: 135.744, confidence interval: 27.055-681.074; $p<0.005$).

Conclusion: Iron deficiency and euthyroid goiter are common subclinical conditions in the Turkish population. In the presence of subclinical diseases followed without treatment, the duration of drug effects may be prolonged. Prospective and more comprehensive studies are needed on this subject.

Keywords: Adenosine, cerebral vasodilation, iron deficiency, euthyroid goiter, myocardial perfusion scintigraphy

INTRODUCTION

Myocardial Perfusion Scintigraphy (MPS) is a conventional imaging method applied in many nuclear medicine clinics (1). Personalized protocol selection is possible within the indicated indications. In cases where exercise stress is not possible or insufficient, pharmacological stress protocol is applied. Adenosine, a vasodilator agent, is frequently used for this purpose in nuclear medicine clinics. Adenosine causes different and widespread effects in different tissues through A1, A2a, A2b, and A3 receptors. It acts through the A1 and A2a receptors in the central nervous system. It exerts diffuse inhibition of neuronal activity. It also acts by inducing vasodilation and increasing the distribution of metabolic substrates (2). Due to its different effects on many tissues, its side effects are usually short-lived. However, these effects are also taken into account when determining the contraindications of the drug (1). The complaints of hot flushes, headache, and nausea which are common during the application, continue for up to 1 hour in some patients. Adenosine is an

endogenous nucleoside found in all cells of the body. Side effects are short-lived as it is rapidly degraded to inosine and adenosine monophosphate (AMP) (3).

Iron deficiency (ID), which is common in the population, is often not treated unless it causes low hemoglobin (Hb) (3). In our retrospective study, we investigated whether euthyroid goiter (EG) followed without treatment and ID without anemia contribute to prolonged and disturbing adenosine complaints.

MATERIALS AND METHODS

Our study included 183 patients with atypical chest pain who underwent MPS to investigate the presence of coronary artery disease. A pharmacological stress agent, adenosine, was administered to all patients for stress imaging. Thyroid ultrasonography (USG) was performed in our patients within one month and they had at least 6-month thyroid function tests (TFT) values. Hb, iron, saturated transferrin (TSAT), and serum ferritin (SF) values of our patients were checked. Those with perfusion defect as a result of MPS, those with chronic diseases, those with chronic drug use and smoking, migraine, diabetes mellitus, chronic or acute inflammation, those with Hb below 12 g/dl, those with TFT disorders, patients who experienced major side effects such as AV block, myocardial infarction, hemorrhagic or ischemic cerebrovascular accident during adenosine infusion were excluded from the study. Before adenosine infusion, patients were fasted for at least 3 hours. They did not ingest caffeine and theophylline-containing foods for at least 12 hours prior to the test.

Adenosine infusion was administered intravenously at a rate of 140 µg/kg/min for 6 minutes. Complaints that occurred during intravenous administration of adenosine were questioned. The presence of at least three of the most common complaints of flushing, headache, nausea, and feeling of ill feeling was considered to have prominent complaints (PC). If these complaints continued for at least 30 minutes, the presence of prolonged prominent complaints (PPC) was accepted. Patients who developed PPC were categorized as group 1 and patients without PPC as group 2. Electrocardiography (ECG) and blood pressure monitoring were performed during the adenosine administration. Our retrospective study was approved by Gaziosmanpaşa Training and Research Hospital Ethics Committee with 70 numbers on 08.06.2022.

Statistical Analysis

Normally distributed variables were expressed as mean ± standard deviation, non-normally distributed variables were expressed as median (min-max), and categorical variables were expressed as a number of cases and percentage. Mann-Whitney U was used to compare non-normally distributed variables, and the K-square test was used to compare categorical variables. The logistic regression analysis method was used to analyze the independent variables determining the development of side effects to adenosine. $P<0.05$ value was considered statistically significant.

RESULTS

159 (86.9%) of our patients were women. There was no significant difference between the two groups in terms of gender (p: 0.879). The mean thyroid gland size in our patients was 15 (11-28) ml. 87 (47.5%) patients had EG. ID was present in 81 (44.3%) patients. PC developed in 96 (52.5%) patients. PPC developed in 51 (27.9%) of 183 patients. There was no significant difference between Group 1 and Group 2 in terms of age ($p = 0.349$). The number of patients diagnosed with EG was significantly higher in Group 1 ($p < 0.005$). Additionally, thyroid size was significantly larger in patients in Group 1 compared to those in Group 2, with respective medians (minimum-maximum) of 20 (11-18) ml and 15 (11-28 ml) ($p<0.005$). In Group 1, 44 (86.3%) patients had iron deficiency, while in Group 2, 37 (28%) patients had iron deficiency ($p<0.005$). The independent variables determining the development of PPC in patients who received adenosine infusion were found to be goiter size (Odds: 1.437, confidence interval: 1.264-1.633; $p<0.005$) and the presence of ID (Odds: 135.744, confidence interval: 27.055-681.074; $p<0.005$). The findings are summarized in Tables 1 and 2.

Table 1. Univariable analysis results in patients with and without prolonged symptoms

	Group 1 (prolonged prominent complaints) n:51	Group 2 (without prolonged prominent complaints) n:132	p
Age	55 (51-59)	56 (51-60)	0.349
Gender (female/male)	44 (86.3%)/7 (13.7%)	115 (87.1%)/17 (12.9%)	0.879
Goiter size (mL)	20 (11-28)	15 (11-28)	0.0005
The presence of goiter (+/-)	8 (15.7%)/43 (84.3%)	88 (66.7%)/44 (33.3%)	0.0005
The presence of iron deficiency (+/-)	7 (13.7%)/44 (86.3%)	95 (72%)/37 (28%)	0.0005

Table 2. Multivariable analysis results in patients with and without prolonged symptoms

	Odds	Confidence Interval	p
Goiter size	1.437	1.264-1.633	0.0005
Iron deficiency	135.744	27.055- 681.074	0.0005

DISCUSSION

Studies on the effects of adenosine on excitable tissues are still ongoing. ECG and blood pressure monitoring are mandatory when applied for pharmacological stress (1). When adenosine is given intravenously, its effect ends in a short time because it is rapidly broken down into its metabolites. PC usually disappears shortly after the end of the infusion. PC is seen in 80% of patients. Flushing is around 40%, headache is around 7%, and nausea is around 7% (1,2). Unexpectedly, we have observed that some of our patients have prolonged these complaints. Although the effect of adenosine ends in a short time, another process it triggers may cause the complaints to last longer. In 6 patients, the complaints did not resolve spontaneously and continued to increase. In these 6 patients, the complaints were resolved with intravenous aminophylline. In some of our patients, side effects continued for up to 1 hour. TFT and Hb values were within normal limits in all our patients. In our study, it was revealed that ID is an independent variable in the occurrence of prolonged side effects of adenosine. ID is common worldwide (3). SF is an acute phase reactant and an important marker of ID. It is known that ID is associated with thyroid diseases. Iron is an essential element for all cell life. Under normal conditions, one-third of transferrin is bound to iron. About 65-75% of iron, which is critical for oxygen transport, is in Hb (4,5). Markers in peripheral blood are important because it is difficult to obtain samples to determine the amount of iron in the tissues (6,7). ID refers to low iron stores that cannot meet the body's iron requirements. The most common presentation is iron deficiency anemia (IDA) (8). Low SF and Hb levels together are very reliable indicators of iron deficiency anemia (9-13). Parameters such as hepcidin, soluble transferrin receptor, and reticulocyte Hb content are not commonly used (14-17). In our retrospective study; SF less than 100 µg/L and TSAT below 20% were considered low. In our study, markers such as hepcidin were not examined in patients. In the case of chronic inflammation, SF increases (18-21). No chronic or acute inflammation was detected in the patients included in our study. Since serum iron levels fluctuate during the day, they are not very valid for diagnosis (21-25). In patients with normal hemoglobin (Hb) levels, if the serum ferritin (SF) is below 30 µg/L in the absence of chronic disease, or if the SF is less than 100 µg/L in the presence of chronic disease, it is considered indicative of ID. For patients with chronic diseases, normal Hb levels, and SF levels greater than 100, the TSAT value is checked. A TSAT value of less than 20% suggests the presence of ID (26). SF levels less than 100 µg/L and TSAT values below 20% are considered diagnostic criteria for ID (27). In our retrospective study; SF below 100 µg/L was considered low. TSAT less than 20% and Hb below 12 g/dl were considered low. Long-term side effects can be reduced if the ID is also treated in patients to whom adenosine will be given. There are studies showing that pial dilatation caused by adenosine occurs through the opening of smooth muscle potassium channels (28-33). These effects have been reported to be mediated by the guanylate cyclase pathway (34,35). A2B receptors are plentiful in the brain and are more active in hypoxia. A3 receptors can modulate the actions of other receptors. A1 receptors cause hyperpolarization of their resting membrane potential. Normally, basal concentrations of extracellular adenosine are sufficient to activate high-affinity A1 and A2A adenosine receptors (35). Stimulant drugs, such as caffeine, act by antagonizing the action of endogenous adenosine. Manipulations that cause the brain's energy demand to exceed its ability to synthesize ATP drastically increase adenosine release (35). In addition, there are studies that argue that adenosine release occurs under conditions where ATP levels should be preserved. Hypoxia inhibits the activity of the adenosine kinase, which converts adenosine to 5'AMP in the heart. This may be the mechanism underlying adenosine release in hypoxia in the brain (35,36). Predicting the side effects that may occur with external adenosine will reduce morbidity. In our study, it was determined that EG and ID increased the frequency of the prolonged effect of adenosine. In most of these two subclinical conditions, the patients are followed without treatment. Adenosine metabolism may take longer than normal in these patients who normally do not have complaints in their daily lives. In conditions such as ischemia, increased adenosine may mediate increasing cerebral blood flow and ameliorating the effects of ischemia. Transient activation of adenosine receptors protects neurons from damage by subsequent hypoxic or ischemic events (36). It is said to be an endogenous anticonvulsant because it increases markedly in seizures (37,38). Changes in arterial CO_2 levels have significant effects on cerebrovascular flow. Hypercapnia causes arterial dilation and increased cerebral blood flow, while hypocapnia causes constriction and decreased blood flow. Even doubling the levels of adenosine in the extracellular fluid can significantly widen cerebral arterioles and increase cerebral blood flow. In general, there is evidence that adenosine is an endogenous mediator between cerebral metabolism and blood flow (37). ID can slow down adenosine removal mechanisms. Thyroid diseases are more common in women (38). The number of female patients was also higher in our study. In a study, 35.9% goiter and 20.2% thyroid nodules were detected in approximately 4000 adults without known thyroid disease (39). It usually becomes visible when the thyroid volume is 40 ml or more (39). Mechanical compression of the trachea or esophagus is present in 30 to 85% of asymptomatic goiter cases (40). This underlying pressure may also have been effective in the complaints of our patients prolonged with adenosine. The weakness of our study is that it is retrospective.

CONCLUSION

ID and EG are common subclinical conditions in the Turkish population. In the presence of subclinical diseases followed without treatment, the duration of drug effects may be prolonged. Prospective and more comprehensive studies are needed on this subject.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The Ethical Approval for the study was obtained from Gaziosmanpaşa Training and Research Hospital Ethics Committee with 70 numbers on 08.06.2022.

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