



Buccal caffeine strips for reversal of adverse symptoms of vasodilator stress

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Background. Due to recurrent shortages of aminophylline, intravenous caffeine has emerged as a commonly used, safe and reliable method to treat adverse effects of vasodilator stress agents. We sought to evaluate the safety and effectiveness of buccal caffeine strips which are rapidly absorbed, inexpensive, readily available, and simplify caffeine administration.

Methods. Consecutive patients undergoing regadenoson stress SPECT MPI were assessed for the occurrence of symptoms during testing over an 11-week period at a single metropolitan hospital. Adverse symptoms, including their severity and duration, were recorded at the time of testing. Patient satisfaction was rated on a scale of 1 to 5 (5 being the most satisfied). Patients received reversal with caffeine if symptoms were felt to be significant enough by the patient and physician performing the test. The treatment received alternated week to week between IV caffeine (60 mg) or 100 mg buccal caffeine strips. Caffeine was given at least 3 minutes after tracer injection. A rescue dose of IV caffeine was offered 10 minutes later if indicated.

Results. Of the 122 patients enrolled in the study, 70 (57%) were included during buccal caffeine weeks and 52 (43%) during IV caffeine weeks, and only 28 (24%) received reversal with a caffeine agent. Seven (6%) received IV caffeine and 21 (17%) received buccal caffeine. There was no significant difference in symptom duration between IV and buccal caffeine after treatment (152.8 vs 163.4 seconds, $P = 0.87$). There was no significant difference in initial and final symptom severity between groups. Only 2 patients in the buccal group required rescue IV caffeine for ongoing symptoms and emesis. None of the IV group required a rescue dose. There was no significant difference in patient satisfaction between the groups (2.8 vs 3.2, $P = 0.38$).

Conclusion. Buccal caffeine strips are a safe, well tolerated, and effective initial strategy to reverse adverse effects of vasodilator stress in the minority of patients who request it. Buccal caffeine alone or with IV rescue caffeine was highly effective in reversing adverse effects and was free of major adverse clinical events. (J Nucl Cardiol 2022)

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Key Words: Vasodilator • Caffeine • Myocardial perfusion imaging

Abbreviations	
SPECT	Single-photon emission computed tomography
MPI	Myocardial perfusion imaging
GI	Gastrointestinal
IV	Intravenous
PO	Oral/by mouth

INTRODUCTION

The use of vasodilator stress for single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has become increasingly common compared to exercise stress. Vasodilators include adenosine, dipyridamole, and regadenoson which all work directly or indirectly through adenosine receptor activation. Side effects are common, with large trials demonstrating an incidence as high as 79%-90%, the majority of which are mild and include dyspnea, flushing, chest discomfort, and headache.¹ More serious side effects include hypotension, bronchospasm, and atrioventricular block.

Methylxanthines such as aminophylline, theophylline, and caffeine are all competitive inhibitors of adenosine at the adenosine receptor and can be used to reverse the effects of these vasodilator stressors.² Due to recurrent shortages of aminophylline, caffeine has emerged as a commonly used, safe and reliable method to treat adverse effects of vasodilator stress agents.³ Oral caffeine is an appealing option in terms of storage, however, consumption of a caffeinated beverage may not be the optimal mode of delivery while acutely symptomatic and may lead to inconsistent dosing of caffeine. Intravenous caffeine is not completely straightforward in its use as it requires compounding, must be refrigerated, and once prepared has a shelf life of only 24 hours. Buccal caffeine strips overcome some of these limitations as they are inexpensive, readily available, have a longer shelf life, and are rapidly absorbed.

However, at this time there is not comprehensive literature assessing the use of buccal caffeine, and an additional convenient reversal agent may be of clinical value. Our study aimed to examine the safety and efficacy of buccal caffeine strips in comparison to IV caffeine for the reversal of regadenoson adverse effects.

METHODS

Patient selection and data collected

Consecutive patients undergoing a regadenoson SPECT MPI over an 11-week period (from January

through March, 2020) at Hartford Hospital (an urban, tertiary care medical center) were assessed for the occurrence of symptoms experienced during stress testing as part of a laboratory quality project assessing the feasibility of buccal caffeine use. In a protocol approved by our Institutional Review Board, the prospectively collected patient symptoms were retrospectively reviewed and analyzed. Patients undergoing exercise in combination with vasodilator stress were excluded as well as patients with dementia or altered mental status.

Patients received reversal with caffeine if symptoms were felt to be significant enough by the patient and the physician performing the test. This typically meant that if at any point at least 3 minutes following tracer injection patients experienced an intolerable or overly oppressive symptom which did not quickly resolve, they were given reversal with caffeine. All tests during this time period were supervised by one of three board certified cardiologists in Nuclear Cardiology. The treatment received alternated week to week between IV caffeine (60 mg) or 100 mg buccal caffeine strips (Elite Ops Energy Strips) based on availability. Caffeine was given at least 3 minutes after tracer injection. A rescue dose of IV caffeine was offered 10 minutes later if indicated for persistent symptoms. Patients who crossed over to IV caffeine due to severe gastrointestinal (GI) upset or who required a 10-minute rescue dose had the indication noted.

Adverse symptoms were recorded during the test by the nurse or the physician based on subjective patient assessment. The type of symptom (dyspnea, headache, chest discomfort, flushing, gastrointestinal discomfort, lightheadedness, throat pain or other), the severity of the symptom before and after treatment (graded from 0 to 10 with 10 being the most severe, and patient satisfaction (graded from 1 to 5, with 5 being the most satisfied) were recorded. The total length of the symptoms and length of symptoms after treatment with reversal agent were obtained during the test. Demographic information, cardiovascular risk factors, and stress test characteristics and results were prospectively collected at the time of the stress test.

Stress protocols

Patients were instructed to fast for at least 6 hours prior to the stress test and avoid consumption of any product containing methylxanthines for at least 12 hours prior to the stress test. A standard regadenoson stress protocol as endorsed by the American Society of Nuclear Cardiology was employed.⁷

Statistical analysis

The initial and final side effect symptom severity, total length of symptoms, length of symptoms after caffeine use, and patient satisfaction at the end of the test were compared between the buccal and IV caffeine groups. When there were multiple symptoms, the worst and longest symptoms were used to assess symptom severity and length. Subgroup analysis was performed in those who received therapy versus those who did not receive therapy and in those who received therapy versus those who were symptomatic but did not receive therapy.

Continuous variables are reported as mean \pm standard deviation and categorical data as percentages. Means of continuous variables were compared using a two-tailed *t*-test. Chi-square test or Fisher's exact test for small sample sizes were employed for categorical variables. A *P* value \leq 0.05 was considered significant. Statistical analysis was done with SPSS 25 (IBM).

RESULTS

Over the 11-week period, a total of 302 patients underwent stress testing with SPECT MPI, with 22 (7%) receiving vasodilator stress after inadequate exercise and 183 (61%) undergoing vasodilator stress alone. Of these patients, 122 (67%) completed symptom assessment forms. A total of 70 patients presented during the buccal caffeine weeks and 52 presented during the IV caffeine weeks. The mean age of the study population was 64.6 ± 11.7 years with an equal proportion of male and female subjects. These and other demographic characteristics are shown in Table 1. No differences in patient characteristics between the buccal and IV caffeine treatment groups were found.

A total of 81 patients (66.4%) reported side effects after regadenoson administration with no significant difference in prevalence of symptoms between buccal and IV caffeine weeks (Table 2). The most common side effect was dyspnea (44.3%), followed by headache and GI discomfort (7.4%), and chest discomfort (4.1%). Symptoms were similar between patients assigned to either caffeine group regardless of receiving any reversal. No serious adverse events occurred during the study period. The initial and final symptom severity, length of symptoms, and patient satisfaction scores were similar between buccal and IV caffeine groups. Twenty-eight patients (23.0%) received caffeine and most of the study patients, 94 (77.0%), did not.

Of the 70 patients presenting during the buccal caffeine weeks, 44 patients (62.9%) reported side effects after regadenoson administration and 21 (30.0%) of them received buccal caffeine (Table 3). Of the 52

patients studied during IV caffeine weeks, 37 patients (71.2%) reported adverse reactions and 7 patients (13.5%) received IV caffeine. Patients were more likely to receive caffeine on the buccal caffeine weeks than the IV weeks ($P = 0.049$) although there was no significant difference in reported symptoms ($P = 0.59$). Only two patients in the buccal cohort and zero patients in the IV caffeine group required rescue with IV caffeine for ongoing symptoms as per protocol. There was no significant difference in the initial (5.9 ± 2.1 versus 5.2 ± 2.3 , $P = 0.39$) and final (0.6 ± 1.1 versus 0.5 ± 0.9 , $P = 0.18$) symptom severity between the buccal and IV groups (Table 3). The total length of symptoms (279.6 ± 170.2 seconds vs 236.8 ± 115.9 , $P = 0.49$) and the length of symptoms following caffeine administration (152.8 ± 179.3 seconds vs 163.4 ± 84.2 , $P = 0.87$) were not significantly different as well. Intensity of the worst symptoms and duration of longest symptoms in the two caffeine groups were similar. Patient satisfaction also was not significantly different between the two caffeine groups (2.8 ± 1.0 vs 3.2 ± 0.8 , $P = 0.38$) as noted in Table 3.

Comparing the 28 patients (23.0%) who received caffeine reversal to the 94 patients (77.0%) who did not found no significant differences in demographics or cardiac risk factors (Online Tables 4 and 5). While initial symptom severity was similar (5.8 ± 2.1 vs 5.0 ± 2.0 , $P = 0.07$), the final symptom severity was lower in the group not receiving therapy (1.1 ± 1.4 versus 0.5 ± 0.9 , $P = 0.008$). The total length of symptoms was 270.8 ± 160.2 seconds in the caffeine therapy groups which was significantly longer than the group not requiring therapy (163.4 ± 84.9 , $P < 0.0001$). The length of symptoms based on treatment received can be seen in Figure 1. Patient satisfaction was also lower in the caffeine patients compared to those not receiving reversal (2.9 ± 1.0 vs 4.3 ± 0.7 , $P < 0.0001$).

DISCUSSION

This study was performed to evaluate the safety and efficacy of buccal caffeine to reverse adverse symptoms caused by regadenoson in the context of frequent shortages of the most widely used reversal agent, aminophylline.³ Randomized controlled trials have demonstrated that aminophylline is safe, well tolerated, and effective in improving overall patient satisfaction when used in conjunction with vasodilator stress testing.^{4,5} Another xanthine derivative, theophylline, has been reported to reverse adverse symptoms of vasodilator stressors safely and effectively, but suffers from both shortages of supply as well as the limitation that larger volumes of medication must be given in order to reach effective doses.⁶ Caffeine represents another option for a

Table 1. Comparison of patient demographics in buccal versus IV caffeine groups

	All patients N = 122	Buccal weeks N = 70	IV weeks N = 52	P-value (buccal vs IV)
Age (years)	64.6 ± 11.7	66.0 ± 12.0	63.0 ± 11.0	0.16
Gender				0.40
Male	60 (50.0%)	39 (56.5%)	21 (41.2%)	
Female	60 (50.0%)	30 (43.5%)	30 (58.8%)	
BMI	31.2 ± 7.1	31.0 ± 7.3	31.6 ± 6.8	0.64
Number of patients with side effects	81 (66.4%)	44 (62.9%)	37 (71.2%)	0.59
Cardiac risk factors				
Diabetes	49 (40.2%)	31 (44.3%)	18 (34.6%)	0.79
Hypertension	91 (74.6%)	56 (80.0%)	35 (67.3%)	0.17
Congestive heart failure	19 (15.6%)	10 (14.3%)	9 (17.3%)	0.84
High cholesterol	84 (68.9%)	53 (75.7%)	31 (59.6%)	0.09
Smoking	68 (55.7%)	42 (60.0%)	26 (50.0%)	0.36
Family history of CAD	58 (47.5%)	31 (44.3%)	27 (51.9%)	0.51
Known CAD	27 (22.1%)	18 (25.7%)	9 (17.3%)	0.38
Resting LVEF (%)	65.7 ± 16.3	66.7 ± 16.9	64.3 ± 15.4	0.42
Post-stress LVEF (%)	65.9 ± 15.1	66.6 ± 15.6	64.8 ± 14.6	0.52

reversal agent. Buccal caffeine offers potential benefits in its availability, low cost, ease of administration, lack of refrigerated storage requirements, and absence of a requirement to prepare doses. This study has demonstrated comparable efficacy of buccal caffeine to IV caffeine to improve symptom severity, symptom length, and patient satisfaction associated with regadenoson stress.

In a previously published series of 241 patients, Doran et al demonstrated the effectiveness of both IV and oral caffeine in the form of cola or coffee in comparison to aminophylline.^{7,8} Oral caffeine was found to be an effective reversal agent for regadenoson side effects for patients who did not have GI upset or suspected intolerance of PO caffeine due to severe symptoms. In the only previous publication using buccal caffeine, Matangi et al demonstrated that buccal caffeine was an acceptable alternative to aminophylline for the reversal of dipyridamole, however, that study only documented hemodynamic changes and did not comment on its ability to reverse adverse effects.⁹ In a similar manner to oral caffeine, buccal caffeine has now been shown to be a safe and effective alternative to IV caffeine. However, advantages of buccal caffeine include low cost, high availability, simple and efficient administration without preparation time, consistent dosing, and rapid absorption. Consuming 12 fl oz of cola or preparing a hot caffeinated beverage would be more time consuming to reach an effective plasma

concentration of caffeine than via the buccal route. Neither oral or buccal caffeine would be acceptable alternatives to an IV medication when reversing gastrointestinal side effects such as nausea or vomiting.

In the current study using alternating weeks of buccal and IV caffeine for reversal of regadenoson, no difference was found in the characteristics of the patients or the symptoms they experienced in each cohort. Initial and final symptom severity, total symptom duration, and symptom duration after caffeine administration were similar in the buccal and IV caffeine groups (Table 3). Worst and longest symptoms and patient satisfaction scores were also similar in the two caffeine cohorts. Understandably, the average patient satisfaction score was lower for patients receiving either form of caffeine compared to patients who did not require reversal given the detrimental effect of side effects on the patient experience. Because no severe adverse symptoms occurred during our study, we cannot comment on the use of buccal caffeine for such reactions and would recommend the use of IV caffeine to reverse severe vasodilator induced adverse symptoms.

This study also argues against the prophylactic use of reversal agents for regadenoson stress. Of the 122 patients, a typical percentage of patients (66%) had adverse symptoms following regadenoson administration, but 94 patients (77%) did not require a reversal agent to treat those symptoms. These figures suggest that a large majority of patients can avoid receiving an

Table 2. Adverse regadenoson symptoms in buccal and IV caffeine patient groups

	All patients N = 122	Buccal caffeine N = 70	IV caffeine N = 52	P-value (Buccal vs IV)
Number of patients with side effects	81 (66.4%)	44 (62.9%)	37 (71.2%)	0.44
Side effects				
Dyspnea	54 (44.3%)	28 (40.0%)	26 (50.0%)	0.84
Headache	9 (7.4%)	5 (7.1%)	4 (7.7%)	1.0
GI discomfort	9 (7.4%)	4 (5.7%)	5 (9.6%)	0.49
Chest discomfort	5 (4.1%)	3 (4.3%)	2 (3.8%)	1.0
Lightheadedness	3 (2.5%)	3 (4.3%)	0 (0%)	0.26
Flushing	1 (0.8%)	1 (1.4%)	0 (0%)	1.0
Throat pain	3 (2.5%)	1 (1.4%)	2 (3.8%)	0.57
Other	4 (3.3%)	1 (1.4%)	3 (5.8%)	0.31
All symptoms				
Initial symptom severity	5.3 ± 2.1	5.3 ± 2.1	5.3 ± 2.1	1.0
Final symptom severity	0.74 ± 1.1	0.77 ± 1.2	0.71 ± 1.1	0.78
Total length of symptoms (seconds)	202.5 ± 128.3	202.4 ± 149.2	202.6 ± 93.6	0.99
Length of symptom after caffeine (seconds)	-	137.7 ± 179.3	148.4 ± 84.2	0.69
Only worst and longest symptom				
Initial symptom severity	5.6 ± 2.1	5.6 ± 2.1	5.6 ± 2.2	1.0
Final symptom severity	0.74 ± 1.1	0.74 ± 1.0	0.75 ± 1.6	0.97
Total length of symptoms (seconds)	204.6 ± 130.7	208.8 ± 161.8	200.7 ± 94.4	0.75
Length of symptom after caffeine (seconds)	-	157.2 ± 176.4	140.9 ± 88.5	0.54
Patient satisfaction	3.9 ± 1.0	4.0 ± 0.8	3.8 ± 1.1	0.25

additional medication during testing which adds to the complexity of the procedure. Also, reversal agents given too soon after the administration of radiotracer run the risk of prematurely reducing hyperemia and falsely decreasing the size of stress perfusion defects.

Limitations

The study was limited by its single center nature and may not be universally applicable as the tendency to use reversal agents following vasodilator stress is often institution dependent. The study also only used regadenoson as the stress agent, and as such does not provide direct data on the reversal of dipyridamole or adenosine. Although the goal was to complete symptom assessment on all consecutive patients during this time period, a third of potentially appropriate patients did not have data collected, especially on weekends, which constitutes a

potential bias. As a whole, the patients without symptom assessment were similar in age and gender to the overall population. Data collection was started just prior to the start of the COVID-19 pandemic which affected the length of the study and the number of patients included given the change in practice necessitated by the pandemic. As a result, the small sample size of patients who received a reversal agent has likely underpowered the comparison between routes of caffeine administration and does not allow for a conclusion on buccal caffeine's use for severe vasodilator induced adverse symptoms. As the study was not blinded, the awareness of the staff about the use of buccal caffeine which was a new and novel reversal agent possibly lead to an increase in the use of caffeine in buccal caffeine weeks. The greater ease of use of the buccal strips and the additional hurdle of having to prepare the IV caffeine may also have contributed to the discrepancy in usage.

Table 3. Comparison of adverse regadenoson symptoms in patients who received buccal versus IV caffeine

	Received buccal N = 21	Received IV N = 7	No therapy N = 94	P-value (buccal vs IV)
Common side effects				
Dyspnea	12 (57.1%)	2 (28.6%)	40 (42.6%)	0.38
Headache	5 (23.8%)	1 (14.3%)	4 (4.3%)	1.0
Chest discomfort	4 (19.0%)	1 (14.3%)	4 (4.3%)	1.0
GI discomfort	3 (14.2%)	3 (42.8%)	6 (6.4%)	0.14
Lightheadedness	2 (9.5%)	0 (0%)	3 (3.2%)	1.0
Flushing	1 (4.8%)	0 (0%)	6 (6.4%)	1.0
Throat pain	1 (4.8%)	0 (0%)	3 (3.2%)	1.0
Other	3 (14.2%)	2 (28.6%)	2 (2.1%)	0.57
All symptoms				
Initial symptom severity	5.9 ± 2.1	5.2 ± 2.3	5.0 ± 2.0	0.39
Final symptom severity	1.3 ± 1.4	0.6 ± 1.1	0.5 ± 0.9	0.18
Total length of symptoms (seconds)	279.6 ± 170.2	236.8 ± 115.9	163.4 ± 84.9	0.49
Length of symptom after caffeine (seconds)	152.8 ± 179.3	163.4 ± 84.2	-	0.87
Only worst and longest symptoms				
Initial symptom severity	6.2 ± 2.1	5.6 ± 2.2	5.3 ± 2.0	0.52
Final symptom severity	1.2 ± 1.2	0.7 ± 1.3	0.6 ± 1.0	0.36
Total length of symptoms (seconds)	307.1 ± 174.4	223.4 ± 118.3	164.1 ± 85.4	0.56
Length of symptom after Caffeine (seconds)	180.5 ± 184.3	179.4 ± 100.0	-	0.91
Patient satisfaction	2.8 ± 1.0	3.2 ± 0.8	4.3 ± 0.7	0.38

Length of Symptoms Based on Treatment Group

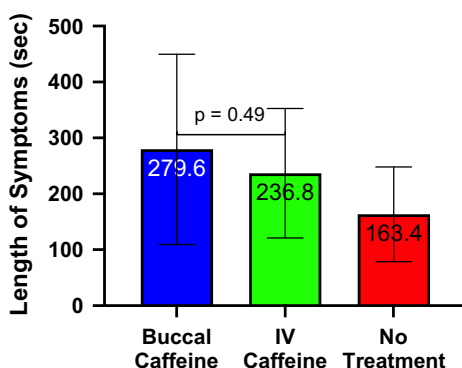


Figure 1. Total length of symptoms based on treatment received.

CONCLUSION

The use of buccal caffeine for the reversal of regadenoson adverse reactions is safe and effective. Buccal and IV caffeine provided similar relief of regadenoson induced adverse symptoms including symptom severity and duration, and similar patient satisfaction scores. Rescue IV caffeine was needed in only two patients receiving buccal caffeine, and no serious adverse reaction occurred in this study. With its many advantages of low cost, ready availability, ease and efficiency of administration, and effectiveness associated with favorable patient satisfaction, we find buccal caffeine is an acceptable alternative to aminophylline or IV caffeine for the management of adverse effects caused by vasodilator stress.

Disclosures

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