

Purpura and bleeding due to calcium channel blockers: A preliminary study

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Abstract

Objective To estimate the frequency of purpura and bleeding in patients on calcium channel blockers and association between calcium channel blocker therapy and petechiae due to capillary fragility induced by Hess test.

Methods A facility based cross-sectional study was conducted involving 60 adult patients only on calcium channel blockers (CCBs) for cardiovascular causes for at least 3 months duration. All the patients were questioned about the spontaneous occurrence of purpura and were examined for purpura. Hess test was performed in all the subjects and the result noted. Patients also underwent investigations to rule out other causes of purpura or bleeding.

Results None of the 60 hypertensive patients included in our study who were only on amlodipine, a calcium channel blocker, had any history suggestive of or examination findings suggestive of spontaneous bleeding or occurrence of purpura. Abnormal Hess test was also not seen in any of the subjects. Platelet count, bleeding time, clotting time and prothrombin time, the key investigations in cases of bleeding disorders were all normal in all the subjects.

Conclusion The results of our study showed that treatment with calcium channel blockers (CCBs), particularly amlodipine, is not related to purpura or bleeding. Our study also shows that therapy with the CCB amlodipine is not associated with petechiae due to capillary fragility induced by Hess test.

Key words

Purpura, bleeding, calcium channel blockers, amlodipine.

Introduction

Calcium channel blockers (CCBs) are among the most frequently prescribed drugs for the treatment of cardiovascular diseases like hypertension, angina pectoris, cardiac arrhythmias, left ventricular diastolic dysfunction, Raynaud's phenomenon, etc.¹ The main effect of CCBs is vasodilation with lowering of the blood pressure. Few case reports

suggest that CCBs precipitate intracerebral bleeding² or may predispose to other hemorrhagic problems like gastrointestinal^{3,4,5} or surgical bleeding.⁶ Calcium channel blockers may cause vasculitis as their side effect.⁷ There are also reports of CCBs like diltiazem causing lichenoid purpura,⁸ and amlodipine causing petechia.⁹ Rarely CCBs, like amlodipine, may also produce thrombocytopenia due to the development of amlodipine-dependent antibodies against platelets.¹⁰

The only study till date seeking a true association between CCBs and purpura and bleeding included 19 patients on CCBs of whom 16 had had either abnormal Hess results or

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marked acral purpura after a Hess test which led the authors to suggest that the high frequency of purpura shown in their study was a pharmacological class effect rather than idiosyncratic reaction. They also suggested that purpura due to CCBs may be due to the vasodilating action of these drugs along with a platelet function abnormality as suggested by abnormal Hess test. Purpura in patients taking these drugs may be a clue to diagnosis of internal or postsurgical bleeding. They concluded that purpura related to calcium channel antagonists is underestimated and that further studies are needed to identify the mechanism by which this occurs.¹¹ Based on only this study, Rook's textbook of dermatology mentions that calcium channel blockers have a class effect of provoking purpura by Hess testing, with occasional clinical bleeding without a change in the platelet count.¹²

We undertook the study to verify the findings of the study by Cox *et al.*¹¹ which suggest that CCBs are related to bleeding, purpura and abnormal Hess test. We selected patients only on CCB therapy to avoid confounding effects of other drugs to avoid the drawback of the study by Cox *et al.*¹¹ which included patients on multiple drugs. If the association between CCB therapy and bleeding, purpura or abnormal Hess test could be established, it can help us to warn patients on CCBs about their increased risk of bleeding. If the association is ruled out, then this study would establish the safety of CCBs with reference to bleeding and purpura.

This study aimed to estimate the frequency of purpura and bleeding in patients on calcium channel blockers and to look for an association between calcium channel blocker therapy and petechiae due to capillary fragility induced by Hess test.

Methods

After approval by the institutional ethics committee, this study was conducted as a Short Term Studentship project-2013 under the Indian Council of Medical Research, in the departments of General Medicine and Dermatology in Indira Gandhi Medical College & Research Institute (IGMC&RI), Puducherry, from 1st May, 2013 to 30th June, 2013. It was a facility-based cross-sectional study which included 60 consenting adult patients on calcium channel blockers only, for at least 3 months for cardiovascular causes, attending the general medicine and dermatology outpatient departments. Whereas patients below 18 years of age, patients concurrently taking any other medication, pregnant and lactating women were all excluded from the study.

Procedure The patients were enrolled into the study obtaining a written informed consent to participate in the study. Strict confidentiality about the patients' details was maintained at all times. Relevant data like age, sex, occupation, details of the cardiovascular illness including details of CCB therapy, spontaneous bleeding manifestations if any, the results of complete blood count, bleeding time, clotting time and prothrombin time and Hess test were recorded in a proforma.

Hess test Hess testing is used to look for capillary fragility. To perform this test, pressure was applied to the upper arm with sphygmomanometer cuff inflated to 10 mmHg above the diastolic level for 5 minutes to produce a standardized increase in capillary pressure. After removing the cuff the number of petechiae in 5 cm diameter circle of the area just below the antecubital fossa was counted. Up to five petechiae are considered normal and more than five petechiae indicate capillary fragility.¹³

Data were entered into Microsoft Office Excel

spreadsheet and computer based analysis was done using SPSS (version 20, SPSS Inc. Chicago, Illinois, USA), Unpaired Student's t-test was done to compare means of various groups.

Results

Clinical profile of the patients Of the 60 patients, 13 (21.7%) were men and 47 (78.3%) were women. The mean age of women was 53.6 ± 8.9 years and the mean age of men was 60.6 ± 10.5 years. Men were significantly older. All the 60 patients who participated in the study were diagnosed with hypertension as their only medical condition. The duration of hypertension varied between 3 months and 20 years. Amlodipine was the only calcium channel blocker that was prescribed for all the patients included in our study. The duration of amlodipine therapy varied between 3 months and 20 years.

History suggestive bleeding/purpura None of the 60 patients reported any history suggestive of bleeding such as gastrointestinal bleeding (melena or hematemesis), hematuria, intracerebral bleeding or bleeding into the skin or bleeding of the gums. None of the 60 patients had undergone any surgery, and hence, postsurgical bleeding could not be commented upon.

Examination findings On detailed examination of the skin and mucosa, we could not detect any purpura or pigmented purpuric dermatoses or purpuric drug eruption or bleeding of the gingiva in any of the 60 patients.

Hess test findings On performing Hess test, none of the 60 patients showed any Hess test abnormality.

Complete blood count, bleeding time, clotting time and prothrombin time were normal except for significantly lower hemoglobin in women when compared with men.

Discussion

When we analyzed our observations we found that all the 60 patients included in the study group were diagnosed with hypertension as their cardiac cause for receiving calcium channel blocker therapy. This could be because hypertension is the most common cardiovascular condition for which patients seek therapy. The criteria we chose were also strict about patients taking only calcium channel blocker therapy and no other concomitant drugs, so that their confounding effects could be avoided. Hence, other patients with co-existing morbidities like diabetes mellitus, ischemic heart disease were excluded from the study as they would be on multiple drugs.

We also found that all the 60 patients who were on CCB therapy were being treated with amlodipine. The reason for this is, amlodipine is the only CCB that is available free of cost in our hospital for the management of hypertension. The other antihypertensive drug that is available free of cost is atenolol, a beta blocker. Patients on a combination of calcium channel blocker and beta blocker were also excluded from the study, to avoid the confounding effect of beta blocker as a cause of bleeding or purpura.

The association between CCBs and bleeding has always been a controversial one.

In our study, none of the 60 patients on CCBs reported any history suggestive of internal bleeding such as gastrointestinal bleeding (melena or hematemesis), or hematuria, or intracerebral bleeding. This finding differs from

studies by Pahor *et al.*³, Rodriguez *et al.*⁴ and Kaplan *et al.*⁵

Analysis by Pahor *et al.* showed a greater risk of gastrointestinal hemorrhage for CCBs compared with beta blockers. The adverse effect was postulated to result from CCB-mediated inhibition of platelet aggregation and of protective vasoconstriction in response to hemorrhage. The inference derived by Pahor *et al.*³ had had lot of shortcomings. β -Blockers, the reference category in this study, protect against gastrointestinal bleeding, which could account for the higher CCB risk ratios observed therein. Misclassification of drug exposure, reflected in the study by Pahor *et al.*³ implausibly low bleeding risk associated with nonsteroidal anti-inflammatory drugs, makes residual confounding by these agents in the sicker population prescribed CCBs difficult to discount.

Study by Kaplan *et al.*⁵ also suggested an increased risk of gastrointestinal hemorrhage with CCBs even though their results were compatible with chance. Similar to the Pahor *et al.*³ study, even this study suffered from the same shortcoming i.e. β -blockers, the drugs with protective action against gastrointestinal bleeding, were the drugs in the reference group.

Study by Rodriguez *et al.*⁵ have also documented increased risk of gastrointestinal hemorrhage with CCBs. But this study failed to demonstrate the decrease in bleeding risk with time after discontinuation of CCBs and this may reflect uncontrolled confounding or bias.

Much of the data on CCBs and bleeding is at odds with the findings of increased risk of gastrointestinal hemorrhage.

The findings in our study were similar to those of observational studies by Pilotto *et al.*,¹⁴ Suissa

et al.,¹⁵ Smalley *et al.*¹⁶ and Kelly *et al.*¹⁷ which did not demonstrate the increased risk of gastrointestinal bleeding attributable to CCBs.

In our study, none of the 60 patients on amlodipine, a calcium channel blocker, gave any history of spontaneous bleeding into the skin presenting as purpura or petechiae or bleeding of the gums. Detailed examination of the skin and mucosa of all the patients did not reveal any purpura, petechiae or bleeding gingivae.

In our study, Hess test was performed in all the 60 patients and none of them showed any abnormality or petechiae.

Our findings are in stark contrast with the results of the pilot study by Cox *et al.*¹¹ who found that of 19 patients on CCBs, 16 had either abnormal Hess results or marked acral purpura after a Hess test, whereas abnormal Hess test was seen only in 2 of 13 control subjects. They also observed that the patients taking diltiazem generally had more petechiae than those taking nifedipine. They even suggested that purpura, either spontaneous or provoked is a pharmacological class effect rather than idiosyncratic and this may be a clue to diagnosis of internal or postsurgical bleeding. They conclude that purpura related to CCBs is probably underestimated and further studies are needed to identify the mechanism by which this occurs.¹¹ The drawbacks of this study are: only 5 of the 19 patients in their study group were not taking any other concomitant medication. The others were on concomitant beta-blockers or angiotensin-converting enzyme (ACE) inhibitors or a combination of beta-blockers and ACE inhibitor or nicorandil or long-acting nitrates or aspirin or furosemide. Even the authors acknowledged the fact that patients did not discontinue other medications during the test procedure, as it was considered potentially dangerous and unethical and they conceded that

other drugs might have contributed to, or been a cause of purpura in some cases. The other factors predisposing to lower leg purpura like elderly patients or those with lower leg edema or venous eczema also applied to some of their patients and even these cannot be discounted while attributing the occurrence of purpura to CCBs alone.

In the same article the authors also reported 4 cases of purpura or internal bleeding due to calcium channel blockers. Two of those patients who had purpura were on treatment with nifedipine. In one patient the purpura disappeared after stopping nifedipine, while the other patient did not wish to alter her medication. The third patient, who was on amlodipine, had Schamberg's disease along with hematuria and hematospermia. When amlodipine was stopped and replaced by an ACE inhibitor, the bleeding tendency rapidly resolved without recurrence. The last patient was on diltiazem, nicorandil and aspirin and she presented with purpura and Hess test demonstrated dramatic purpura.¹¹

Kuo *et al.*⁷ reported a patient who developed purpura due to vasculitis while on nifedipine therapy, which disappeared after discontinuation of nifedipine but recurred when diltiazem was initiated.

Inui *et al.*⁸ reported a patient who developed lichenoid purpura while on diltiazem and disappearance of the lesions after diltiazem was discontinued.

Murthy *et al.*⁹ reported a patient on amlodipine for treatment of essential hypertension for a period of six months who developed petechiae over both the lower limbs. These petechiae disappeared completely after amlodipine was substituted with enalapril.

The results of no purpura or Hess test abnormality in our study could be attributed to the strict inclusion criteria of patients only on CCBs and no other drugs for including patients into the study, so that the confounding effect of the concomitant drugs have been avoided. Our study has clearly shown that amlodipine, the calcium channel blocker is not related to bleeding or purpura either spontaneous or Hess test provoked.

The other reason could be that since all the patients included in our study were only on amlodipine and not any other CCBs like diltiazem, verapamil, nifedipine or nimodipine, the tendency for the drugs other than amlodipine, belonging to the various classes of CCBs to cause purpura or Hess test abnormality, if present, could not be evaluated in our study.

Ioulios *et al.*¹⁸ in their review of literature of the spectrum of cutaneous reactions associated with calcium antagonists, have described about flushing, peripheral edema, gingival hyperplasia, facial telangiectasia, photosensitivity reactions, psoriasiform eruptions, acute generalized exanthematous pustulosis, hypersensitivity syndrome, exfoliative dermatitis and Stevens-Johnson syndrome, subacute cutaneous lupus erythematosus, pemphigus and pemphigoid, erythromelalgia, gynecomastia and oral ulcers.¹⁸ There is no mention of purpura as an adverse effect of CCBs in the article, except for the case report of lichenoid purpura possibly caused by diltiazem by Inui *et al.*⁸

While analyzing all the case reports, what strikes us the most is that in spite of millions of patients taking various calcium channel blockers on a regular basis for their cardiac condition for many years, only a handful of case reports are available that relate CCBs to bleeding and purpura. This suggests that purpura, either spontaneous or provoked by Hess test, due to

CCBs is not a common phenomenon and it is unlikely to be a pharmacological class effect of these drugs.

Conclusion

The results of our study suggest that the calcium channel blocker amlodipine is not related to bleeding or purpura, either spontaneous or provoked by Hess test. However, to make a generalization that whether or not CCBs are related to bleeding or purpura, and Hess test abnormality, studies with a larger sample size should be conducted which include patients on different classes of CCBs, excluding patients on any other drugs which can confound the results.

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