

openheart Comparison of various calcium antagonist on vasospastic angina: a systematic review

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ABSTRACT

Background Coronary artery vasospasm is an abnormal spasm of coronary arteries that cause transient or complete occlusion without exertion. It causes stable angina to ACS. However, this can be prevented by calcium channel blockers (CCBs) which suppress Ca^{2+} influx into the vascular muscle cells. Nevertheless, several CCBs adverse effects are harmful for these patients. Selecting the right CCBs would give the best clinical practice.

Method The studies were obtained from four major medical databases by various keywords. Inclusion and exclusion criteria were implemented as adult >18 years, observational study, English language and drug of interest. Duplicates were eliminated, and the remaining studies were reviewed. Final full-texts assessment was conducted independently by Newcastle-Ottawa Scale and Revised Cochrane.

Results The search found 1378 articles. However, six studies were selected after implementing the study criteria. Diltiazem was found to decrease angina and increase quality of life until 12th week of treatment; however, some adverse effects include atrioventricular block and recurrent angina up till 4th week were found. Meanwhile, nifedipine was found to decrease vasospastic angina (VSA) by the fourth and eighth weeks of treatment. Nevertheless, it caused excessive drop in BP and increase heart rate by eighth week. In addition, slow-release preparation of both CCBs were found to increase efficacy and compliance. Lastly amlodipine was also found to decrease VSA by $17\% \pm 140\%$ and 33% after 6 weeks, but further studies needed.

Conclusion Diltiazem, nifedipine and amlodipine are potent in decreasing VSA, however, tailoring specific CCBs adverse reactions to patient condition and the drug preparation would be substantially beneficial for the outcome.

INTRODUCTION

Coronary artery vasospasm (CAVS) is described as an abnormal constriction of coronary arteries that may cause complete or transient occlusion of the vessel and is not influenced with exertion.¹ This phenomenon is known as several terms, such as variant angina, Prinzmetal's angina or vasospastic angina (VSA). The mechanical pathophysiology of this vasospastic disease is

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ CCBs which suppress Ca^{2+} influx into the vascular muscle cells are known to prevent symptoms of VSA.#

WHAT THIS STUDY ADDS

⇒ This study finds evidences that the drug preparation and tailoring patient's clinical characteristics to the specific CCB would increase the effectiveness of treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In clinical practice, using diltiazem would benefit VSA patients by decreasing symptoms of VSA and increasing quality of life until 12th week of treatment. However, due to its adverse reaction, it is best suited for tachycardic tendency patients with normal BP. Meanwhile, Nifedipine is beneficial to decrease VSA by the 4th and 8th weeks of treatment. Nevertheless, it is best administered in elevated BP and bradycardic tendency patients due to its adverse reaction. In addition, the long-acting preparations are found to increase efficacy and compliance, especially in treating the early morning symptoms.

⇒ Although amlodipine shows some benefits in suppressing VSA, further research is needed to determine its clinical use.

due to coronary spasm that can cause acute ischaemia and present itself ranging from stable angina to acute coronary syndrome.^{1,2} There are plethora of factors that can influence with the development of the disease such as autonomic nervous system, inflammation, oxidative stress, endothelial dysfunction, genetic and lifestyles.¹ Although the prognosis is relatively favourable, sudden death can still be ensued.² Based on 'Guidelines for Diagnosis and Treatment of Patients With VSA' by Japanese Circulation Society in 2013, calcium channel blockers (CCBs) that function by suppressing Ca^{2+} influx into vascular smooth muscle cells are proven to be effective in preventing VSA.³

CCB is considered to be the first choice of drug for the treatment of VSA. The 2014

non-ST elevation acute coronary syndrome (NSTEMI-ACS) guidelines recommend either a dihydropyridine (DHP) (eg, amlodipine, nifedipine) or non-DHP (eg, verapamil, diltiazem) alone or in combination with long-acting nitrates.⁴ Verapamil, diltiazem or nifedipine are the choices of CCB for initiation for newly diagnosed VSA. The main concerns of using these drugs are the adverse effects. DHP CCBs caused peripheral vasodilating, while non-DHPs have negative chronotropic effects that can cause bradycardia and atrioventricular (AV) conduction delay. Non-DHP can therefore be harmful in patients with history of heart failure with reduced ejection fraction.⁵

The current systematic review was initiated to determine which CCBs (nifedipine, diltiazem or amlodipine) gives the best clinical outcome in terms of symptoms relief and side effects. This review may aid healthcare workers in choosing which CCBs to be used when faced with patient presented with VSA.

METHODS

Study selection and search strategy

A systematic literature search on PubMed, SCOPUS, Cochrane Library databases and EMBASE Databases was conducted by two investigators (AE and MK) to find all potential relevant studies before May 2021. Keywords used in the search terms were: 'Adult' with 'calcium channel blocking agent', 'calcium antagonist', 'calcium channel blocker', 'calcium channel blockade', 'calcium channel antagonist', 'calcium inhibit', 'calcium block', 'calcium channel blocking drug', 'CCB', 'dihydropyridine', 'non-dihydropyridine', 'antihypertensive drug', names of specific calcium antagonists of interest (diltiazem, amlodipine and nifedipine) combined with 'prinzmetal's variant angina', 'variant angina', 'PVA', 'coronary artery vasospasm', 'CAVS', 'coronary artery spasm', 'CAS', 'vasospastic angina', 'VSA' and 'frequency of symptomatic episodes', 'serious complications', 'recurrence', 'recurrent'. The flow of the search strategy was described in figure 1. The two authors manually and independently screened through the articles on the Journals mentioned.

Inclusion and exclusion criteria

Studies were screened for eligibility based on our inclusion criteria for this current systematic review. Any type of observational study (case-control, nested case-control or cohort study) investigating the potency of CCBs on reducing frequency of symptomatic episodes and serious complications of VSA in adults (>18 years) were included in this literature search. Animal experimentation, literature reviews, editorials, commentaries, case reports and conference abstracts were excluded in this literature search. Moreover, medications not related to the study, patient with age less than 18 years old, and studies published in language other than English were excluded.

Data extraction

Once the literature search concluded and duplicates were eliminated, the two investigators (AE and MK) reviewed

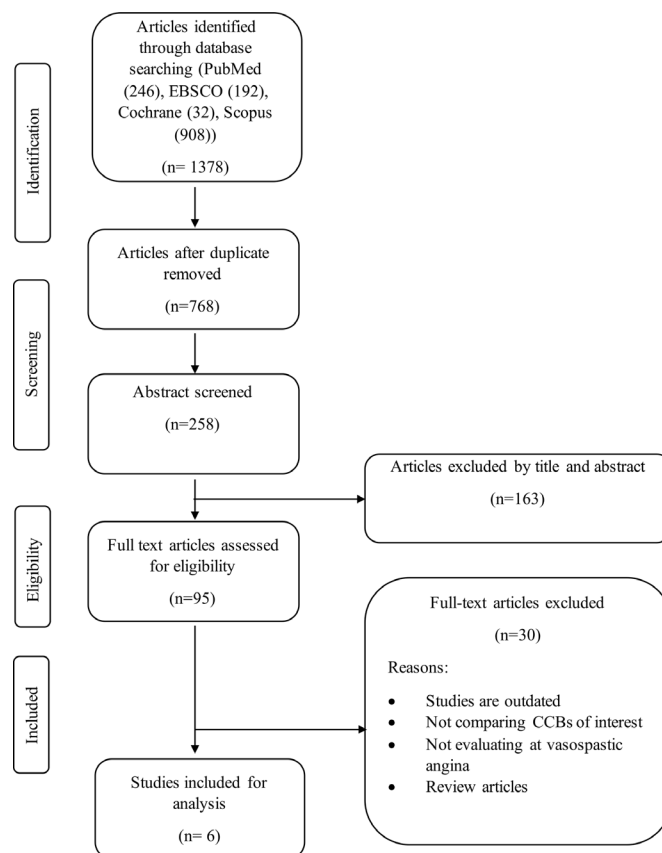


Figure 1 PRISMA flow diagram of studies included in the systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

each article independently. Discrepancies in assessment by each investigators were discussed and consulted with the third investigator (JS) until an agreement was achieved by consensus. Full-text articles that met the inclusion criteria and passed the reviews were obtained and all the required information and data were extracted and assessed independently.

Quality assessment

Selected articles were independently assessed by two investigators (AE and MK) using Newcastle-Ottawa scale (NOS) and revised Cochrane. NOS score equal or greater than seven was classified as high-quality articles, this assessment tool is used for case control and cohort studies. Whereas assessment of the systematic review was conducted by Revised Cochrane tool, in which the flow chart will determine the paper's quality.

RESULTS

Search results

The literature search from four different databases including PubMed, EBSCO, Cochrane and Scopus gathered 1378 number of articles. These search hits were screened for duplication which resulted in the remaining 65 articles. The title and abstract of these studies were further screened and excluded due to confounding factors, type and year of the studies which left six articles.

The remaining studies' full text were assessed for their eligibility. An expert opinion paper, papers before the year 2000, a case reports, a paper without specific type of CCB comparisons were excluded. In total six studies were selected for further analysis.

Study characteristics

The study characteristics are shown in online supplemental table 3. Most of the studies came from Korea (3/6), whereas the remaining two studies were conducted in Japan, and a single study was from China. The research participants varied, ranging from 5 to 2741 people. A single study by Park *et al* included male subjects only, whereas all the other studies included both gender with male predominance except for a study by Shin *et al* that studied both genders equally. All studies examine the clinical symptoms of VSA by angiography with either ergonovine or acetylcholine provocation test. Studies by Gao *et al*, Higuma *et al*, Oikawa *et al* also included Holter ECG. The clinical symptoms of VSA were also assessed by Seattle Angina Questionnaire in a study by Kook *et al*.

The efficacy and impact of the different types of CCBs on VSA

Action of various types of CCB on VSA are depicted in online supplemental table 4. The studies' participants varied from 5 to 2741 patients. The studies showed that Diltiazem decrease the frequency of chest pain in VSA patients, and increase the quality of life based on the Seattle Angina Questionnaire.^{2,6} However, in a study which participants consumed Diltiazem for VSA, recurrent angina up till fourth week and asymptomatic AV block were found in a single separate patient.²

Studies also found that nifedipine is a potent agent in treating VSA. Its effect in decreasing the frequency of angina was evidently found by the fourth and eighth weeks of treatment. However, it was also noticed to cause excessive drop in blood pressure in a patient, and increased in heart rate by eighth week.^{2,7} Both nifedipine and diltiazem were apparently effective by the fourth weeks of treatment. Nevertheless, diltiazem showed a better tendency in reducing the frequency of VSA in the 12th week.² In addition, studies that applied the slow release form of nifedipine once a day and diltiazem twice a day seemed to increase compliance and efficacy to decrease frequency of VSA.

Amlodipine is another CCB which was found to improve symptoms in VSA patients. The study showed that it decreased the mean frequency of weekly chest pain by 17.6%±140.1%. The proportion of chest pain free patients after 6 weeks study period was 33%. Several adverse effects which were gathered including headache (20%) as the most common, followed by dizziness (8.3%), palpitation (8.3%), bradycardia (4.2%), chest discomfort (4.2%), GI symptoms (4.2%).⁸

Quality assessment

The quality assessments of the studies were depicted in online supplemental table 1 using NOS format, and

online supplemental table 2 using the revised Cochrane format for systematic reviews. Among the two studies assessed by NOS, the study by Park *et al* was qualified as a good study, and the study by Gao *et al* was considered poor quality.^{9,10} Furthermore, among the four studies assessed by Revised Cochrane, three studies were considered high risk,⁶⁻⁸ and a study by Higuma *et al*, was assessed as having some concern.²

DISCUSSION

CCBs have been used as the first line treatment for VSA. They non-competitively block voltage-sensitive L-type calcium ion channels in coronary smooth muscle that cause vasodilation on coronary arteries. They can be categorised based on their mechanism of action: DHP such as amlodipine and nifedipine, phenylalkylamines such as verapamil, and modified benzothiazepines such as diltiazem. Despite knowing CCBs had been documented to relieve and prevent VSA, little was known as to which CCB would provide the most effective relieve while considering the safety as well. This systematic review aimed to expand our understanding about which CCBs would be best suited in patients with VSA and its confounding symptoms. Despite being common and involved in many clinical scenarios like stable angina, acute coronary syndrome and arrhythmia, VSA often times being missed in the diagnosis. This may also be due to provocative tests that were rarely performed. Therefore, the prevalence rate for VSA was highly dependent on which population was being studied as well as the initiative of clinicians in investigating VSA with the provocative tests.¹¹ Additionally, few recent studies were found to be investigating on the treatment of VSA, which led us having six studies that met the inclusion criteria and all of the studies were conducted in Asian regions only (Korea, Japan, China).

Among the included studies, all of them showed that diltiazem, nifedipine and amlodipine reduced the clinical symptoms and recurrence of VSA significantly. Kook *et al* evaluated diltiazem through the use Seattle Angina Questionnaire, comparing from baseline to 12 weeks after treatments. Significant improvement was found in the overall study population with changes in the total score by 5.2±8.5 (p=0.0002). However, no significant difference was found in the frequency of angina attacks (a subscale of the Seattle Angina Questionnaire) when comparing baseline with treatment groups. On the contrary, Park *et al* showed that treatment with diltiazem presents with just 8.3% recurrent of angina attack within 5 years. A number of studies were in line with what we found that diltiazem is effective in reducing the frequency of angina episodes and increasing exercise tolerance, which is likely due to its potent dilator effect on coronary arteries.¹²⁻¹⁴ This effect is also seen in terms of the artery diameter change in which Kook *et al* showed the magnitude of improvement in artery diameter change with the use of diltiazem and shown to have the greatest improvement among other

intervention groups (nebivolol and low dose combination of nebivolol and diltiazem).

Higuma *et al* found significant reduction in the frequency of angina baseline value per week with nifedipine continuous release (CR) (a long-acting once-daily formulation of nifedipine, with a dose 1×40 mg) and diltiazem R (a sustained-release formulation of diltiazem, with dose 2×100 mg) in a 4th, 8th and 12th weeks of study. Nifedipine (CR 1×40 mg) is also evaluated by Oikawa *et al* that showed significant decrease in angina frequency per week in the eighth week treatment. There are not many recent articles that discuss nifedipine on VSA. We managed to find an old case report from 1978 that showed nifedipine was effective in managing VSA. Duration of its protective effect was proportional with the dose, and its effect potentiate with the combination use of nitroglycerin. They also observed myocardial infarction could be caused by intense and prolonged coronary vasoconstriction, which was why nifedipine combined with nitroglycerin were necessary to prevent it.¹⁵

Amlodipine also showed similar results given by Shin *et al*, with a change of 17.6% in the frequency of weekly chest pain. Nifedipine is well known to have strong vasodilatory and antihypertensive effects with little influence on myocardial contraction.² Amlodipine has an excellent blood pressure lowering effect and should be used as the first choice in the treatment of VSA who need blood pressure control. The long-acting effect also gives an advantage to facilitate patient's compliance in adhering to the treatment without the trouble of multiple daily doses.¹⁶ Peripheral oedema was the only adverse event often seen in patients treated with amlodipine. Once daily dose (adjustable from 5 to 15 mg) was found to be both safe and effective.¹⁷

Various studies of CCB on angina showed unique adverse reactions and confounding results of the drugs. Studies of nifedipine CR 40 mg by Higuma *et al* found that significant heart rate increment in the eighth week of treatment, which might be beneficial in the bradycardia patients. Meanwhile, it was also found to cause excessive drop in blood pressure in a study by Oikawa *et al*, which would be beneficial in anginal patients with hypertension.²⁷

Diltiazem which comes from the non-DHP group showed several other unique adverse reactions. The study by Park *et al* and Higuma *et al* showed that incidence of AV block was significantly increase in diltiazem usage, and another study found an asymptomatic advanced AV block. However, this incidence could be decreased by combination with nitrate therapy significantly as depicted in the study by Park *et al*. This drug is thought to be beneficial for pounding palpitation, tachycardia and rhythm control patient with predisposing anginal attack.²¹⁰

Amlodipine which was previously discussed to have limited recent studies of its efficacy on anginal attack, was found to cause several adverse reactions. The most common symptoms were headache by 20% followed with dizziness by 8.3%. However, the overall adherence of

amlodipine treatment in anginal attack was good, only a single subject had the adherence of less than 80% in the study by Shin *et al*. In addition, amlodipine was also found to decrease the glyceryl trinitrate consumption in the study.⁸

Beside all the common CCBs, a study also observed the adverse reaction of benidipine 4 mg two times per day. However, only half of the study population had improvement, and 21% of the subjects had aggravated anginal attack. In fact, a patient was found to have >40 attacks on day 11 during the drug treatment. All in all, based on the evidence available, there are not enough benefits to recommend this type of CCB to patients with variant angina.⁷

Subjects' compliance to the CCB therapy for the variant angina is closely associated with the frequency of drug administration. The study by Morikami *et al* showed that both first generation nifedipine and diltiazem were not able to suppress the early morning symptom of variant angina. However, further development of CCB such as Nifedipine slow release (L) taken two times per day was able to eliminate the morning variant angina symptoms. This was followed with a newer generation CCB, such as nifedipine CR, which is administered once daily. This drug was found to increase compliance especially for chronic variant angina therapy as administered just once daily. This CR preparation was also able to decrease the adverse reaction of nifedipine such as palpitation and increase in heart rate. This is because it causes less stimulation on autonomic nervous system. Following nifedipine, diltiazem has also got a newer generation extended-release preparation termed diltiazem R, however it is still administered two times per day.^{18 19}

Limitation

Several limitations of this systematic review included the number of recent studies which investigated CCBs for variant angina were confined. This is true as there were six studies included after thorough screening of various medical databases. Furthermore, these studies had some risk of bias. This included comparability, deviation of intention, outcome measurement and selection of report result. However, all the papers were randomised and the paper by Park *et al* was interpreted as a good quality according to NOS.

CONCLUSION

It can be concluded that major CCBs such as diltiazem, nifedipine and amlodipine are potent agents to decrease the VSA symptoms. However, the drug adverse reaction and preparation may modify the overall treatment outcome. Patients with elevated heart rate tendency and normal control of blood pressure will benefit the most from diltiazem. Meanwhile, patients with decrease heart rate tendency and elevated blood pressure will benefit the most from nifedipine. In addition, nifedipine CR once daily and diltiazem R two times per day are not only

effective in increasing the patient compliance, but also effective in suppressing the early morning VSA symptom. Other CCBs such as amlodipine showed some benefits in suppressing VSA but needs further investigation.

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