Treatment of complicated and uncomplicated hypertension with nifedipine in Palestine

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ABSTRACT

Objective: It is generally agreed that short acting calcium channel blockers (CCB) as nifedipine are not safe as the reflex increase in sympathetic activity and thus, their use in hypertension (HTN) is questionable. The objective of this study was to determine the extent of utilization of short acting nifedipine in the treatment of complicated and uncomplicated HTN in one of the major districts in Palestine, Nablus.

Method: The data for this study were collected from patient's medical files. Data collection was made over a period of 6 months (April - October 2003) in Nablus, Palestine. The sample studied included 876 patients with cardiovascular diseases. Focus was made on the 262 patients with uncomplicated HTN and the 147 patients with both HTN and diabetes mellitus.

Results: A total of 247 (28.2%) patients in the study sample were receiving CCB. One third (33.7%) of patients with uncomplicated HTN were receiving CCB mainly as monotherapy with most of them (61%) were receiving the old generation nifedipine as a short acting formulation. Use of nifedipine was also more common among elderly patients above the age of 60 years.

Conclusion: There was a tendency to use short acting nifedipine as antihypertensive monotherapy among patients with either uncomplicated or complicated HTN. This irrational use needs to be reviewed since it is associated with higher risks.

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Calcium channel blockers (CCB) are chemically a diverse group of drugs that share the common property of blocking the transmembrane flow of calcium ions through voltage-gated L-type (slowly inactivating) channels.[1] The CCB are among the most frequently prescribed drugs for the treatment of hypertension (HTN), angina and arrhythmia.[2,3] At least, 9 CCB drugs are approved for clinical use namely; the dihydroperidine (DHP) drug class like nifedipine, nicardipine, isradipine, amlodipine, felodipine and nisoldipine; the non-dihydroperidine (non-DHP) drug class like verapamil and diltiazem. However, only the following are available in the Palestinian market: nifedipine, amlodipine, felodipine, verapamil and diltiazem.

Currently, there is no clinical studies showing benefit of CCB in reducing morbidity and mortality among patients with HTN. In fact, the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) advocates the use of beta blockers (BB) and diuretics as first line therapy based on the fact that these are the only classes of drugs that have demonstrated benefits in morbidity and mortality when used to treat patients with HTN.[4] Calcium channel blockers are recommended as first-line therapy for HTN only if there is a compelling reason not to administer a thiazide diuretic or BB.[5] Although unconvincing to few scientists, several retrospective case control studies have suggested that treatment of HTN with primarily short acting CCB may be associated with an increased incidence of myocardial infarction.[6-10] The suggested potential

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mechanism for the cardiovascular complications attributed to CCB may be the reflex sympathetic stimulation of ß-adrenergic receptors. This reflex sympathetic over stimulation occurs after administration of short acting DHP, but not the longer acting ones, in normal subjects and patients with HTN.[11-13] Calcium channel blockers are considered a neutral option for the treatment of HTN associated with diabetes mellitus (DM) as they do not adversely affect glucose metabolism, lipid metabolism, or renal function.[14] However, CCB cannot be considered as first line therapy among diabetic hypertensive patients due to the increased vascular risk and due to the well documented benefit of angiotensin converting enzyme inhibitors (ACE-I) among this category of patients.[15-17] Some placebo controlled studies of diabetic hypertensive patients showed that the DHP calcium antagonists did not slow the progression of proteinuria or renal failure, but verapamil and diltiazem did.[18,19] The association between CCB utilization and cancer among hypertensive patients is still controversial. Some studies have indicated that older patients who were taking CCB had a higher risk of cancer than those who were taking BB or ACE-I.[20] Other studies showed that there is an increase in the risk of breast cancer among women who were taking CCB compared to women who were not.[21] Other studies in other countries disagree and showed no effect of CCB therapy on the risk of developing any type of cancer.[22–24]

A summary of all clinical reports on CCB suggest that CCB may be associated with: (1) an increase in the risk of myocardial infarction and mortality in patients with HTN or coronary artery disease especially in patients taking higher daily dosages particularly immediate release nifedipine;[25-27] and (2) an increase in the risk of gastrointestinal hemorrhage and cancer in the elderly.[28,29] Based on this, the short acting nifedipine should be used with great caution (if at all), especially at higher doses in the treatment of HTN, angina and myocardial infarction.

In Palestine, the Palestinian National Authority is the main provider of health services. The United Nations Relief and Works Agency and other Non-governmental Organizations have considerable contribution to the health sector in Palestine. Recent Palestinian health surveys showed that 44.4% of the population in the West Bank, Palestine, have governmental health insurance and get their medications from governmental clinics. The objective of this study was to determine the extent of use of CCB in general and nifedipine, in particular, among patients with either complicated or uncomplicated HTN.

Methods. The study was carried out in Nablus district, the largest district in north Palestine, with a population of 325,269 inhabitants.[30] The medical files of 876 patients who were diagnosed with cardiovascular diseases were reviewed and analyzed. These files were selected randomly from the 4 governmental out-patient primary health care centers in Nablus district in north Palestine. These health care centers provide medical services to patients registered at the Ministry of Health (MOH) as chronic patients and who dispense their medications on regular basis. In each primary health care center, every other file was obtained and if it belongs to a patient with a cardiovascular disease, it is considered part of the study. Files that belong to patients suffering from non-cardiovascular diseases were not included for the study. The total number of files present at the 4 centers where the study took place was more than 8,000 files. Eight hundred and seventy six medical files fit the criteria and were considered for the study. In each medical file, the data regarding age, gender, drug history (all drugs prescribed for the patients) and the prescribing physician were obtained and analyzed using Statistical Package for Social Sciences version 10. Data collection was made over a period of 6 months starting April - October 2003. The researchers took permission from the Ministry of Health officials before starting the collection of data.

Results. ***Characteristics of the sample and CCB utilization pattern.*** Medications prescribed for the 876 patients suffering from various types of cardiovascular diseases were investigated. In this project, focus was made on CCB in general and nifedipine in particular among patients having either complicated or uncomplicated HTN. Data regarding patients with complicated HTN were analyzed but emphasis was made on hypertensive patients with DM. The majority of the patients were having either complicated or uncomplicated HTN suggesting that HTN is the most common type of cardiovascular disease in the sample studied. A total of 247 (28.19%) patients in the study sample were receiving CCB. Gender analysis of the patients receiving CCB medications were 122 (49.39%) men and 125 (50.6%) women suggesting that there is no gender preference in prescribing CCB among patients with cardiovascular diseases. Analysis of diseases for which CCB were prescribed showed that these medication were prescribed for uncomplicated and complicated HTN as well as complicated and uncomplicated cardiovascular diseases as shown in **Table 1**. One third (122/362; 33.7%) of patients with uncomplicated HTN were receiving CCB while lesser percentage of diabetic hypertensive patients were receiving CCB (31/174; 17.8%).

Age distribution of patients receiving CCB. Analysis of the age distribution of the patients receiving CCB shows that more than 50%

Table 1 - Cross tabulation of cardiovascular diseases in the sample and CCB utilization.

Cardiovascular diseases seen among the 876 patients	CCB				Total
	Yes		No		
	n	(%)	n	(%)	
Uncomplicated HTN	122	(33.7)	240	(62.3)	**362**
HTN + DM	31	(17.8)	143	(82.2)	**174**
HTN + other cardiac diseases	43	(39)	67	(61)	**110**
Other complicated and uncomplicated CV diseases	51	(22.2)	179	(77.8)	**230**
Total	247	(28.2)	629	(71.8)	**876**

CCB - calcium channel blockers, HTN - hypertension, DM - diabetes mellitus, CV - cardiovascular

of the patients receiving CCB were elderly patients whose age is above 60 years while less than 15% of the patients were below 50 years of age.

Types of CCB used by patients in the sample study. Nifedipine and diltiazem were the most commonly used types of CCB followed by amlodipine and verapamil. Diltiazem is not extensively used among patients with complicated or uncomplicated HTN. The high percentage of diltiazem utilization among the total sample is due to the extensive use of diltiazem among patients with other complicated and uncomplicated cardiovascular disease especially ischemic heart diseases (IHD).

Utilization of CCB among patients with uncomplicated hypertension. Patients with uncomplicated HTN were treated with either monotherapy or combination of antihypertensive therapy. The antihypertensive drug classes used most commonly were BB, thiazide diuretics, ACE-I, CCB and others. Approximately 78% (282/362) of those patients with uncomplicated HTN were treated with single anti-HTN drug (monotherapy). Drug classes used most commonly as monotherapy for the treatment of uncomplicated HTN were, in ranking order: BB (94/282), ACE-I (87/282), CCB (83/266) and others as thiazides or prazosin (18/282). Calcium channel blockers were used as monotherapy or combination therapy by approximately one third (122/362; 33.7%) of the patients suffering from uncomplicated HTN. Eighty three (83/122; 68%) patients with uncomplicated HTN were receiving CCB as monotherapy. Analysis of the types of the CCB used as monotherapy by patients with uncomplicated HTN revealed that approximately 61.44% (51/83) were receiving the old generation DHP CCB nifedipine as a single agent. Other types of CCB, both DHP and non-DHP class as amlodipine (12%) and verapamil (5%) were also used, but to a lesser extent than short acting nifedipine. Further analysis of the type of nifedipine used as monotherapy by patients with uncomplicated HTN showed that approximately 88% of the patients were using the short acting type of nifedipine rather than the longer, slow-release type. As a summary, out of the 122 patients receiving CCB, 51 patients were using short acting nifedipine as monotherapy and 46 patients were using sustained release nifedipine monotherapy.

Calcium channel blockers utilization among patients with complicated hypertension. Focus is made here on patients with HTN complicated with DM, diabetic hypertensive (HTN + DM). The total number of patients in the study sample who were having HTN complicated with DM was 174 (19.86%). Those diabetic hypertensive patients were treated with either monotherapy or combination therapy. The antihypertensive drug classes used most commonly both in mono and combination therapies of diabetic hypertensive partner were ACE-I, BB, thiazide diuretics, CCB and others. Analysis of antihypertensive medications used by those patients indicated that combination therapy is common (108/174). However, approximately 38% of those diabetic hypertensive patients were on monotherapy treatment mainly as ACE-I. Although, CCB are considered favorable antihypertensive drug class among diabetic hypertensive patients given their lack of effect on both glucose and lipid metabolism, CCB, both as in monotherapy and combination therapy were used among less than 17.81% of diabetic hypertensive patients (31/174). Again, the short acing nifedipine type were the most common type of CCB used by this group of patients. Several studies indicated that ACE-I drug class is the safest for hypertensive patients with DM. In our sample, ACE-I were the most common drug class followed by BB and CCBs were ranking behind in the overall utilization of antihypertensive medications.

Discussion. Recent publications by the Palestinian Bureau of Central Statistics (PBCS) have shown that HTN is the most prevalent chronic health condition in Palestine, when compared to other chronic diseases.[31] This indicates the importance of the proper management and rational selection of antihypertensive drug therapy in order to improve the overall health of the Palestinian population. Few published studies were carried out in the Arab world to assess this issue. A comparison of our findings to that published in neighboring countries as well as in other countries is shown in **Table 2.** Despite JNC-VI recommendations and the warning issued by the FDA, National Heart, Lung and Blood Institute (NHLBI), and WHO/ISH

Table 2 - Comparison of published data regarding CCB utilization among hypertensive patients with those in Palestine.

Reference	Country where the study took place	Conclusion
Current study	Palestine	There is a tendency to use short acting CCB (nifedipine) among both complicated and uncomplicated HTN.
35	Bahrain	Nifedipine formulations were the most extensively prescribed CCBs and almost half of the CCB-treated patients were on immediate release-nifedipine, whereas IR-diltiazem and IR-verapamil, and amlodipine were infrequently prescribed.
36	Bahrain	The general principles of geriatric pharmacotherapy and the guidelines for antihypertensive combinational therapy were poorly followed.
37	Bahrain	There are substantial differences between family physicians and general practitioners in terms of preference for different drug classes for the management of diabetic HTN and that there was suboptimal compliance among both family physicians and general practitioners to international recommendations.
38	Czech Republic	Consumption of short-acting nifedipine in the 4 years after recognition of its risks still remains very high suggesting that implementation of clinical trial results to clinical practice is very slow and ineffective.
39	USA	The prescribing pattern of BB, CCB, ACE-I and thiazides for hypertensive patients were in sharp contrast to the JNC VI guidelines.
40	Canada	A study using administrative database containing information on more than 1.2 million elderly patients have found that simplified practice guidelines for HTN did not have notable effects on prescribing pattern on Ontario.

CCB - calcium channel blockers, HTN - hypertension, BB - beta-blockers, ACE-1 - angiotensin converting enzyme inhibitors, JNC VI - Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure.

Table 3 - Summary of studies used to evaluate antihypertensive medications among diabetic hypertensive patients.

Reference	Name of Study	Conclusion
41	*Losartan Intervention for Endpoint Reduction* (LIFE) study.	Suggested that ATII-RA might even be superior to beta-blockers in reducing cardiovascular morbidity and mortality among diabetic hypertensive patients.
42	*Captopril Prevention Project* (CAPPP)	Found that ACE-I inhibitors were superior to diuretics and BB in treating diabetic hypertensive therapy.
43	*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial* (ALLHAT)	Showed that diuretics and ACE-I are almost equivalent in all aspects when used in treatment of diabetic hypertensive patients.
44	*The United Kingdom Prospective Diabetes Study* (UKPDS) and *Swedish Trial in Old Patients with HTN – 2* (STOP-2).	Indicated that ACE-I, diuretics and BB were equivalent in reducing cardiovascular events and mortality among diabetic patients.
45	*Heart Outcomes Prevention Evaluation* (HOPE)	Suggested that ACE-I need to be the first line therapy for treatment of HTN among DM patients.

CCB - calcium channel blockers, HTN - hypertension, BB - beta-blockers, ACE-1 - angiotensin converting enzyme inhibitors, ATII RA - angiotensin II receptor antagonist.

Guidelines Subcommittee concerning the poor safety of short acting formulations of nifedipine,[32,33] our data shows that there is a tendency to use short acting nifedipine CCB as monotherapy among patients with uncomplicated HTN. Furthermore, more than half of the patients receiving CCB were above the age of 60 years. The age factor is very important and should limit the tendency to use the short acting nifedipine CCB. In elderly patients, short acting nifedipine can potentially lead to an increased risk of myocardial infarction especially in patients with subclinical forms of coronary artery diseases.

There are a growing number of pharmacological treatment options for patients with HTN. Several studies have been carried out (**Table 3**) to evaluate the best therapy for diabetic hypertensive patients, which mostly suggest that thiazide diuretics, ACE-I and ATII-RA are superior to BB and CCB and thus, are preferred as first line therapy while CCB and BB are best used as second or third line treatment for HTN treatment in DM. Although several reports indicated that most diabetic hypertensive patients may require more than one antihypertensive agent to achieve an optimal blood pressure control, approximately, (approximately 38%) were prescribed a single antihypertensive agent (monotherapy). The utilization of the antihypertensive monotherapy regimen among diabetic hypertensive patients may be due to either lack of knowledge or economic reasons. In either case, the suboptimum use of antihypertensive drugs will increase risks of cardiovascular morbidity and

mortality among the patients. CCB ranked third considering both monotherapy and combination therapy of diabetic hypertensive patients. Again, the DHP, short acting nifedipine, was the most commonly prescribed CCB and diltiazem being the least commonly prescribed. Amlodipine and verapamil, were in between. Although, the non-DHP, diltiazem was reported to have positive effects on diabetic proteinuria,[34] it was not popular among diabetic hypertensive patients. ACE-I was the most commonly prescribed drug class both in mono and combination therapy of diabetic hypertensive patients. The use of ACE-I among diabetic hypertensive patients is in accordance with the current recommendations for the management of HTN among diabetic patients. ACE-I are known to have favorable effect on blood glucose level and a renoprotective effect which makes this drug class to be preferred among hypertensive patients with DM. However, the expensive ATII-RA drug class was not prescribed indicating absence of such drug class from the clinics or lack of current knowledge on favorable effects of such drugs on diabetic hypertensive patients or tight control imposed by the authorities on prescribing such expensive drugs.

In conclusion, this study shows that there is a tendency among physicians to prescribe short acting nifedipine for both complicated and uncomplicated HTN. This inappropriate uses of nifedipine will increase the health and economical risk on the patient and the health system. We strongly recommend better drug monitoring for medications among this category of patients as well as patients with chronic diseases. This monitoring could be achieved through appointing skilled pharmacist whose responsibility is to review patient's medication and deliver continuing medical education in the field of current pharmacotherapy.

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