International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Prognosis and Natural History of Drug-Related Atrioventricular Block

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Abstract: ***Drug related AV (atrioventricular) block is an important but poorly defined common clinical problem.Little is known about the natural history and prognosis of patients with drug-related AV block. This study was undertaken to assess the prognosis and natural history of drug related AV block (DRB). Out of 44 consecutive patients with drug related second or third degree AV block,61% of patients had resolution AV block within 48 hours of withdrawal of the drug. However, 40% of them developed a recurrence of AV block despite discontinuation of the culprit drug.Electrocardiographic finding of AV nodal or infranodal block was not a predictor of permanent pacemaker requirement in patients with drug related AV block. Beta-blockers were the most common drugs associated with DRB. Conclusion: Sixty-four percent of patients with DRB had persistent or recurrent indication for permanent pacemaker implantation (PM) in 12 months of follow-up, despite the withdrawal of the culprit drug. DRB is not a benign condition and it needs close follow-up. Drug related AV block is often revealed by, rather than actually caused by the drugs.***

Keywords: Atrioventricular block, Betablocker, Calcium-channel blocker, Prognosis

1. Introduction

Betablockers and non-dihydropyridine calcium channel blockers that slow or block atrioventricular conduction are commonly used in the treatment of hypertension, ischemic heart disease, arrhythmias and heart failure. Therefore, patients may present with atrioventricular block while taking these medications. Drug-related AV block (DRB) is an important but poorly defined common clinical problem. In presence of symptomatic AV block secondary to drug (beta-blocker or calcium channel blocker) treatment, one has to decide whether to stop, reduce the dosage, or continue it if there is no acceptable alternative in which case pacing therapy should be cosidered. Such decisions are presently being made on the basis of clinical judgement, as there are no published guidelines. The prognosis and natural history of the patients with drug related AV blockare not well defined. According to contemporary guidelines, PM implantation is generally considered unnecessary in patients with drug-induced AV block. However, there are few studies that reported significant risk of recurrence of AV block in patients with drug-induced AV block despite the discontinuation of the culpritdrug. Therefore, this study was undertaken to assessthe prognosis and natural history of drug related AV block).

2. Materials and Methods

We retrospectively analyzed 146 consecutive patients referred to our institution between January 2016 and August 2018 with a diagnosis of symptomatic type II second-degree or third-degree AV block. This also includes 44 patients referred to our institution with the diagnosis of AV block while receiving betablockers and non-dihydropyridine calcium channel blockers.In addition, beginning in August 2018, we prospectively collected data from all patients admitted to our institution with the diagnosis of second-degree or third-degree AV block. Patients with concomitant myocardial infarction, vasovagal syncope, electrolyte abnormalities, digitalis toxicity and those taking class I and class III antiarrhythmic drugs were excluded. Patients with atrial fibrillation and bradyarrhythmia were alsoexcluded. Symptoms were defined as the occurrence of fatigue, presyncope and fatigue. The site of AV block was diagnosed by surface electrocardiography. The cause and effect relation between beta-blockers (metoprolol, atenolol, carvedilol and bisoprolol) or calcium channel blocker(verapamil, diltiazem)therapy and AV block was defined according to the response to drug discontinuation. Patients were classified into one of the following three groups:1)AV block developed in the absence of drugs that affect AV conduction (Non-DRB); 2)AV block caused by drugs: AV block that resolved within 48 hours after drug withdrawal and never recurred during the follow-up period. 3) AV block not caused by drugs: AV blocks that persisted or recurred after drug withdrawal.Betablockers and calcium channel blockers were discontinued soon after hospitalization.All patients were monitored continuously during their hospitalization period until the resolution of AV block within 3-5 days or received an implanted pacemaker if AV block did not resolve. Patients with resolution of AV block after discontinuation of drug were discharged and were followed up in out-patient clinic with surface ECG, Holter monitoring and /or External Loop Recorder (ELR) for evaluation of AV conduction. All patients were asked to report their symptoms at their out-patient clinic visits or during telephone interviews. Patients were followed for 12 months and then their data was analyzed.Permanent pacemaker was implanted for all of the patients with recurrence of AV block during follow-up. Collection and analysis of data were authorized by the ethics committee of the hospital.

3. Statistical Analysis

Data were expressed as mean ± standard deviation if continuous and as counts and percent (%) if categorical.

Data analysis was performed using SPSS software package (version 16, SPSS, Inc., Chicago, IL, USA). Student's T test and Fisher's exact probability test were used to analyze the data. P value < 0.05 was considered statistically significant.

4. Results

Baseline clinical characteristics of the patients included in the study are presented in Table 1. Of 146 patients with AV block, who met the criteria and entered the study, 44 (30%) were receiving beta-blocker or calcium channel blocker during the diagnosis of AV block. Thirty-three patients (75%) were on β-blockers: metoprolol (n = 22, 50±13 mg/day), atenolol (n =6, 37.5±12.5 mg/day), carvedilol (n = 3, 6.25 mg/day), bisoprolol (n = 2, 2.5 mg/day). Eleven patients (25%) were on calcium channel blocker: verapamil (n= 7, 85±14 mg/day), diltiazem (n = 4, 90 mg/day). The remaining 102 (70%) patients did not use any beta-blocker or calcium channel blocker at the time of AV block.Patients with drug related AV block were similar to those with AV block occurring in the absence of drugs with regard to the clinical characteristics including underlying diseases, presenting symptoms and left ventricular ejection fraction except for hypertension, which was more common in DRB group reflecting the initial indication for these medications.Both patient groups had similar electrocardiographic characteristics, including the degree of AV block, the ventricular escape rate and QRS duration at the time of presentation (table-2) .Majority of patients had wide QRS with ventricular escape beat less than 40 per minute suggesting infranodal AV block in the two groups with or without medication (84% vs 82%,p=NS).Right bundle branch with left anterior hemiblock was the most common electrcardiographic pattern seen both the groups (37% vs 40%, p=NS).AV block resolved in 61% of the 44 patients with DRB within 48 hours of discontinuation of drug. In contrast, spontaneous improvement of AV conduction within 48 hours of admission occurred in only18% of 102 patients with the diagnosis of AV block in absence of drug therapy (61% vs 18%, p<0.0001). However, 40% of patients with spontaneous improvement of AV conduction after withdrawal of the culprit drug had recurrence of AV block in the absence of drug therapy during one year of follow-up period. Spontaneous recurrence of AV block was similar in both non-DRB and DRB group of patients (40% vs 36%, p=NS). Thus 64% of patients presenting with second or third-degree AV block during therapy with betablocker or calcium channel blockers had persistent or recurrent AV block even after discontinuation of these medications.We didnot find any relationship between QRS duration or ventricular rate or level of AV block and development, persistent or recurrence of AV block in drug users(Table-3).

Table 1: Clinical Characteristics of Patients with Second- or Third-Degree AV Block*

	AV Block During Drug Therapy, (n = 44)	AV Block Without Drugs, (n = 102)	P Value
Age (yrs)	67.2 ±10.7	64.2 ± 10.2	0.11
Males	31(70.4%)	71 (69.6%)	0.94
Pesentation	Syncope, 29 (65.9%) Pre-syncope, 11 (25.0%) Fatigue, 4 (9.0%)	Syncope, 70 (68.6%) Pre-syncope, 24 (23.5%) Fatigue, 8 (7.8%)	0.74 0.84 0.80
Hypertension	34(77.2%)	56(54.9%)	0.010 (S)
Diabetes mellitus	16(36.3%)	31(30.3%)	0.47
Coronary artery disease;	11(25.0%)	22(21.5%)	0.65
LVEF (echo) < 40%	9 (20.4%)	17(16.6%)	0.58

Data are presented as mean ± SD and No. (%).

Table 2: Electrocardiographic Characteristics of Patients with Second- or Third-Degree AV Block*

	AV Block During Drug Therapy, (n = 44)	AV Block Without Drugs, (n = 102)	P value
QRS width > 120 ms.	37 (84.0%)	85(83.3%	0.91
Ventricular rate < 40bpm	39(88.6)%	86(84.3%)	0.49
AV block degree	Second-degree 5 (11.3%)	Second-degree 12(11.7%)	0.94
	Third-degree 39 (88.6%)	Third-degree 90 (88.2%)	0.94
AV block level	AV nodal block 6 (13.6%) Infranodal block 37 (84.0%) Undetermined 1(2.2%)	AV nodal block, 16(15.6%) Infranodal block, 82(80.3%) Undetermined, 4(3.9%)	0.74 0.38 0.18

Data are presented as mean ± SD and No. (%).

Table 3: Characteristics of the patients with AV Block on medication after discontinuation of drugs

	AV block not caused bydrugs. #(n = 28)	AV block caused by drugs. *(n= 16)	P value
Age (yrs)	68.1±11.0	66.2±9.3	0.56
Male	19 (67.8%)	11 (68.7%)	0.95
QRS duration > 120 mcsec.	24 (85.7%)	14 (87.5%)	0.86
Ventricular rate < 40 bpm	24 (85.7%)	13 (81.2%)	0.69
AV block Second-degree	4 (14.2%)	2 (12.5%)	0.86
Third-degree	24 (85.7%)	14 (87.5%)	0.86

Data are presented as mean ± SD and No. (%)
AV block persisted or recured after discontinuation of drug during follow-up.
* AV block regressed after discontinuation of drug and didnot relapse during follow-up.

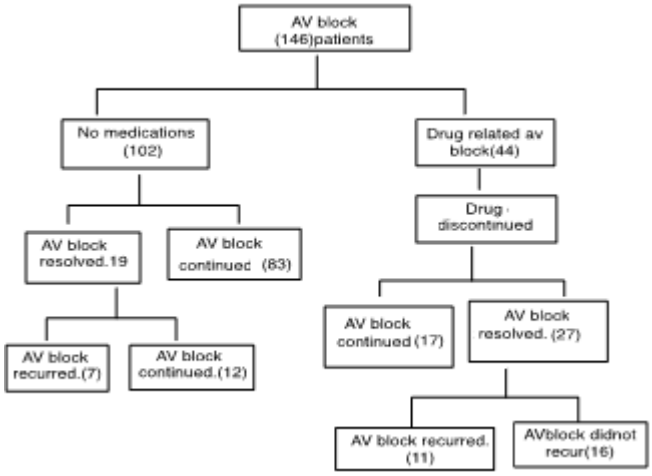

Figure 1: Flow chart describing the course of 146 patients with atrioventricular (AV) block. The number of patients in each step is shown in parentheses.

5. Discussion

The main finding of this retrospectivestudy was that more than one half of the symptomatic patients admitted in the hospital with the diagnosis of DRBhad persistent or recurrent AV block even after the withdrawal of the culprit medication in 12 months of follow-up. This suggests that these AV blocks were not caused by, but actually revealed by drugs. In our study beta-blockers were found to be the most common offending drug involved in the development of AV block. Drugs were discontinued in all of these patients (n=44) but in 17(39%) of them AV block didnot regress. In 27(61%) of them AV block resolved but relapse was observed in 40% of patients in one year of follow-up. Drug-related AV block (DRB) is an important but poorly characterized common clinical problem. In presence of symptomatic AV block secondary to drug treatment, one has to decide whether to stop, reduce the dosage, or continue it if there is no acceptable alternative in which case pacing therapy should be cosidered. Such decisions are presently being made on the basis of clinical judgement rather than published guidelines. According to contemporary guidelines, PM implantation is generally considered unnecessary in patients with drug-induced AV block. However; our findings revealed that 64% of patients with drug related AV block had persistent or recurrent indication for permanent pacemaker implantation even after withdrawal of the medication in 12 months of follow-up. Few other studies reported similar result. Zelster et al. reported that only 15% of AV blocks in patients treated with beta-blockers and/or calcium channel blocker, is truly caused by these drugs. In this study, 52% of patients had AV block that is caused by drugs, and this high incidence of DRB may be due to the inclusion of bradycardic atrial fibrillations and digoxin users. The authors concluded that as these drugs slow down the conduction of AV node, this would prevent rather than provoke conduction block in infranodal pathways, so in these patients, infranodal conduction disease expected to be more severe and sooner or later become permanent. Our patients received therapeutic doses of AV conduction impairing drugs. Significant bradycardia is rare with therapeutic doses of drugs in structurally normal heart, however, they can unmask AV block in those with an underlying latent AV conduction disease. Drugs may act as triggersof concealed AV block because they can unmask AV block in those with an underlying AV conduction disease. Thus when AV block develops in patients taking beta-blockers or calcium channel blockers, the possibility of significant underlying conduction system disease should be considered.

We didnot find any relationship between QRS duration or ventricular rate and development of AV block in drug users. A similar follow-up study recommended pacemaker therapy for all patients on betareceptor blocking drugs and QRS width > 120 ms. ECG finding of AV nodal or infra nodal block was not a predictor of permanent pacemaker requirement in our patients with drug related AV block. However,more than 80% of our patients had QRS>120ms.Although drug related AV block is considered to be reversible, for majority of patients it is unusual for atrioventricular block to reverse with cessation of medications when used at therapeutic doses and even when reversal of atrioventricular block is observed acutely, later a permanent pacemaker implantation is often necessary.

6. Study Limitation

One main limitation of this study is its retrospective design. Elderly symptomatic hospitalized patients were evaluated. Our observations cannot be generalized to asymptomatic, ambulatory or younger patients. We only evaluated symptomatic AV block as a possible indication for pacemaker implantation in this study. Patients with atrial fibrillation and bradyarrhythmiawerealsoexcluded from our study.Since His-bundle recording was not performed in our series; the site of AV block could not be accurately defined.

7. Clinical Implications

Our study suggests that, the majority of patients (64%) with drug related AV block will have persistent or recurrent indication for permanent pacemaker implantation despite withdrawal of culprit drug. Follow-up of these patients is needed.Beta-blockers are the most common drugs associated with the development of AV block.

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