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The Effect of Ivabradine on High Sensitivity C-Reactive Protein Levels and Short Term Clinical Outcome in Patients with Acute Coronary Syndrome

Mathew George[1], Lincy Joseph[2] and Anumol Joseph[2*]

[1]*Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla-689107, Kerala, India*
[2]*Department of Pharmacuetical Chemistry, Pushpagiri College of Pharmacy, Thiruvalla-689107, Kerala, India*

Corresponding author

Abstract

Acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Ivabradine is a new bradycardiac agent acting on the I_f current channels of sinoatrial nodal cells to decrease the rate of diastolic depolarization and thus the heart rate. The primary and principal cause of acute coronary syndrome in more than 90% of the patients is the rupture of an atheromatus plaque, endothelial dysfunction and inflammation and formation of fatty streaks are the core distributors to atherosclerotic plaque formation. High Sensitivity C-reactive protein is a sensitive marker of inflammation. Increased levels of Hs-CRP are associated with endothelial dysfunction, vascular inflammation and in increase cardiovascular risk. The study (n=80) aims to evaluate the effect of Ivabradine on high sensitivity C-reactive protein levels and its effect on ACS therapy. The objective of the study to know the effect of ivabrdine of hs-CRP level and the assessment of cardiac risk. In the study of 80 patients, the patients was categorized into two groups, there is significant reduction of hs-CRP levels, but more significant in the group who is taking Ivabradine. Since P value is less than 0.001, in both groups the level of hs-CRP is significantly reduced. Since P>0.05 at admission there is no significant difference in the mean value of hs-CRP in both the groups. But after discharge the mean values is significantly different (P<0.05) and is concluded that the difference is more in GROUP 1 who is taking ivabradine.

Article Info

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Keywords

ACS, hs-C-reactive protein, Ivabradine, Heart rate, I_F current.

Introduction

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non—ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Acute coronary syndrome is a term used to describe a range of conditions associated with sudden, reduced blood flow to the heart. Unstable angina and NSTEMI are closely related conditions: their pathophysiologic origins and clinical presentations are similar, but they differ in severity (1,2,3,4). A diagnosis of NSTEMI can be made when the ischemia is sufficiently severe to cause myocardial damage that result in the release of a biomarker of myocardial necrosis into the circulation. One condition under the umbrella of acute coronary syndrome is myocardial

infarction (heart attack) — when cell death results in damaged or destroyed heart tissue. Even when acute coronary syndrome causes no cell death, the reduced blood flow alters heart function and indicates a high risk of heart attack. Acute coronary syndrome often causes severe chest pain or discomfort [1]. It is a medical emergency that requires prompt diagnosis and care. Treatment goals include improving blood flow, treating complications and preventing future problems.

Atherosclerosis is the ongoing process of plaque formation that involves primarily the intima of large- and medium-sized arteries; the condition progresses relentlessly throughout a person's lifetime, before finally manifesting itself as an acute ischemic event. Acute coronary syndrome usually results from the build-up of fatty deposits (plaques) in and on the walls of coronary arteries, the blood vessels delivering oxygen and nutrients to heart muscles.

A high-sensitivity C-reactive protein (hs-CRP) test may be used to help evaluate an individual for risk of cardiovascular disease (CVD). It may be used in combination with a lipid profile or with other cardiac risk markers, such as a lipoprotein-associated phospholipaseA2 (Lp-PLA2) test, to provide added information about heart disease risk[21].

The American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups as follows:

1. Low risk: less than 1.0 mg/L
2. Average risk: 1.0 to 3.0 mg/L
3. High risk: above 3.0 mg/L

Ivabradine was approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic HF[27]. Ivabradine is the first drug with a novel mechanism of action acting by selective inhibition of the pacemaker I_f "funny" channel, which is responsible for the autonomic capacity of the sinoatrial (SA) node. I_f current are upregulated in atrial tissue of patients with HF.

Materials and Methods

Study design: A Prospective experimental study

Study population: Patient diagnosed with Acute Coronary Syndrome in cardiac IP Department

Study site

1. Department of Cardiology, Pushpagiri Medical College Hospital, Tiruvalla.

2. Pushpagiri College Of Pharmacy, Tiruvalla

Study period: 6 MONTHS

Sample size of the study: 80 patients.

$N = [2S_P^2 [Z_{1-\alpha/2}+Z_{1-\beta}]^2] / \mu^2_d$
$S_P^2 = S_1^2+S_2^2 /2$

Where,

S_1^2- Standard deviation in the first group.
S_2^2-Standard deviation in the second group.
μ^2_d - Mean difference between the samples.
α -Significance level.
1-β-Power

Study criteria

Inclusion criteria

1. Patients with ischemic manifestations suspected to represent ACS.

2. Patients with sinus rhythm whose heart rate was greater than 60bpm on a resting standard 12 lead ECG.

3. Patients with acute ST segment elevation or non ST segment elevation Myocardial infarction.

4. Patients who are willing to sign the informed consent.

5. Patients of IP patients.

6. Patients of age >18 yrs.

Exclusion criteria

1. Pregnant and breastfeeding women or women of childbearing potential.

2. Patient with atrial fibrillation or flutter, sino atrial block and complete atrio ventricular block.

3. Patient who are not willing to sign informed consent.

4. Patients already on medications with ivabradine

A Prospective experimental study was conducted at Pushpagiri Medical College hospital based on the topic "Effect of Ivabradine on high sensitivity c-reactive protein levels and short term clinical outcome in patients with acute coronary syndrome". 80 patients was selected for the study (2). The selection was based on the inclusion and exclusion criteria. Initially the baseline hs-CRP was taken within 24 hours of admission (before starting ivabradine therapy). The second value of hs-CRP was taken at the time of discharge and it is then followed-up after 4 weeks. The hs-C-reactive protein concentrations were calculated using semiautoanalyser. Morisky medication adherence scale [MMAS] was used to determine the medication adherence (7).

Instrument: Semi autoanalyser.

Reagent used

Diluent (R1): Tris buffer 20mmol/l, pH 8.2 Sodium azide 0.95 g/L.

Latex (R2): Latex particles coated with goat IgG anti-human CRP, pH 7.3, Sodium azide 0.95 g/L.

Determination of hs-CRP

Preparation of blank: Add 10 µl of calibrator solution into a test tube

Preparation of standard: Add diluent (R1) 0.8ml and latex (R2) 0.2ml into a test tube.

Preparation of test: Add diluent (R1) 0.8ml and serum 0.2 ml into a test-tube, Mix and read the absorbance after 4 min

Results and Discussion

In this study, most of the study population falls under the age group 45-79.The patients mostly found in between the age group of 55-70. Out of the 80 patients in this study, majority of ACS patients were males (67.5 %) and remaining were females (32.5%).

Among the 80 enrolled patients in the study, 93.8% patients were married and 6.3% were unmarried. It was observed that only 17.5% patients are having a positive family history and 82.5% were free of risk.

When considering the Educational status of 80 patients, 70% patients were educated, nearly 30% were uneducated, 65.0% were employed and 35% were unemployed.

Out of the 80 patients, 8.8% were having a co-morbidity of heart failure, 73.8% were having a co-morbidity of peripheral arterial disease, 5% were having chronic renal failure, 10.0% were having pulmonary disease, 2.5% were having GIT disorders.

From the total of 80 patients considered in the study, the main cause of acute coronary syndrome was due to hypertension (52.5%), dyslipidemic conditions(46.3%) and diabetic conditions (47.5%) followed by smoking (26.3%), obesity (31.3%), oldage (27.5%).

ADR of Ivabradine when evaluated using narinjo scale of adverse drug reaction, ADR, it is found to be unlikely (76.3%).From the study, it was clear that patient counselling had improved the medication adherence as the P value is less than 0.001 after couselling.MMAS-4 scale was used for medication adherence

Table.1 Distribution of patients based on ADR

ADR	GROUP 1	GROUP 2	Total
Unlikely	29	32	61
	36.3%	40.0%	76.3%
Possible	11	8	19
	13.8%	10.0%	23.8%
Probable	0	0	0
	0.0%	0.0%	0.0%
Definite	0	0	0
	0.0%	0.0%	0.0%
Total	**40**	**40**	**80**
	50.0%	**50.0%**	**100.0%**

Table.2 Distribution of patients based on ACS co-morbidities

ACS CO-MORBIDITIES		GROUP 1	GROUP 2	Total
Heart failure	Count	4	3	7
	% of Total	5.0%	3.8%	8.8%
Peripheral arterial disease	Count	29	30	59
	% of Total	36.3%	37.5%	73.8%
Chronic renal failure	Count	2	2	4
	% of Total	2.5%	2.5%	5.0%
Pulmonary disease	Count	5	3	8
	% of Total	6.3%	3.8%	10.0%
GIT disorders	Count	0	2	2
	% of Total	0.0%	2.5%	2.5%
Total	**Count**	**40**	**40**	**80**
	% of Total	**50.0%**	**50.0%**	**100.0%**

Table.3 Distribution of patients based on aetiology

AETIOLOGY [CAUSES]		GROUP 1	GROUP 2	Total
Hypertension	Count	22	20	42
	% of Total	27.5%	25.0%	52.5%
Diabeties Mellitus	Count	25	13	38
	% of Total	31.3%	16.3%	47.5%
Smoking	Count	10	11	21
	% of Total	12.5%	13.8%	26.3%
Dyslipidemia	Count	15	22	37
	% of Total	18.8%	27.5%	46.3%
Obesity	Count	15	10	25
	% of Total	18.8%	12.5%	31.3%
Positive Family History	Count	6	7	13
	% of Total	7.5%	8.8%	16.3%
Atherosclerosis	Count	17	10	27
	% of Total	21.3%	12.5%	33.8%
Oldage	Count	11	11	22
	% of Total	13.8%	13.8%	27.5%
Unhealthydiet	Count	4	0	4
	% of Total	5.0%	0.0%	5.0%

Table.4 Effect of ACS patient on heart rate

HEART RATE >60 bpm		GROUP 1	GROUP 2	Total
Yes	Count	26	25	51
	% of Total	32.5%	31.3%	63.8%
No	Count	14	15	29
	% of Total	17.5%	18.8%	36.3%
Total	**Count**	**40**	**40**	**80**
	% of Total	**50.0%**	**50.0%**	**100.0%**

Table.5 Effect of ACS patient on ST segment elevation

ST SEGMENT ELEVATION		GROUP 1	GROUP 2	Total
STEMI	Count	28	31	59
	% of Total	35.0%	38.8%	73.8%
NSTEMI	Count	12	9	21
	% of Total	15.0%	11.3%	26.3%
Total	**Count**	**40**	**40**	**80**
	% of Total	**50.0%**	**50.0%**	**100.0%**

Table.6 Effect of ACS patient medication adherence

MEDICATION ADHERENCE		GROUP 1		GROUP 2	
		Before	After	Before	After
High	Count	3	36	2	33
	% of Total	3.8%	45.0%	2.5%	41.3%
Medium	Count	4	29	7	29
	% of Total	5.0%	36.3%	8.8%	36.3%
Poor	Count	29	3	9	3
	% of Total	36.3%	3.8%	11.3%	3.8%
Chi square		***54.862***		***49.9***	
P value		***P< 0.001***		***P< 0.001***	

Table.7 Comparison of HS-CRP level in each group

GROUPS	Hs-CRP LEVEL			P value
	ADMISSION (Mean±SD)	DISCHARGE (Mean±SD)	AFTER 4 WEEKS (Mean±SD)	
GROUP 1	6.48±2.05	3.80±1.30	1.44±1.07	P<0.001
GROUP 2	6.65±1.62	4.39±1.13	2.88±1.14	P<0.001

Table.8 Statistical comparison of HS-CRP level based on risk level

GROUPS	Hs-CRP LEVEL	ADMISSION	DISCHARGE	AFTER 4 WEEKS	P value
GROUP 1	Low risk	0	13	24	p<0.001
	Avg risk	16	11	8	
	High risk	24	16	8	
GROUP 2	Low risk	7	2	9	p<0.001
	Avge risk	10	18	16	
	High risk	23	20	15	

Fig.1 ACS comorbidities

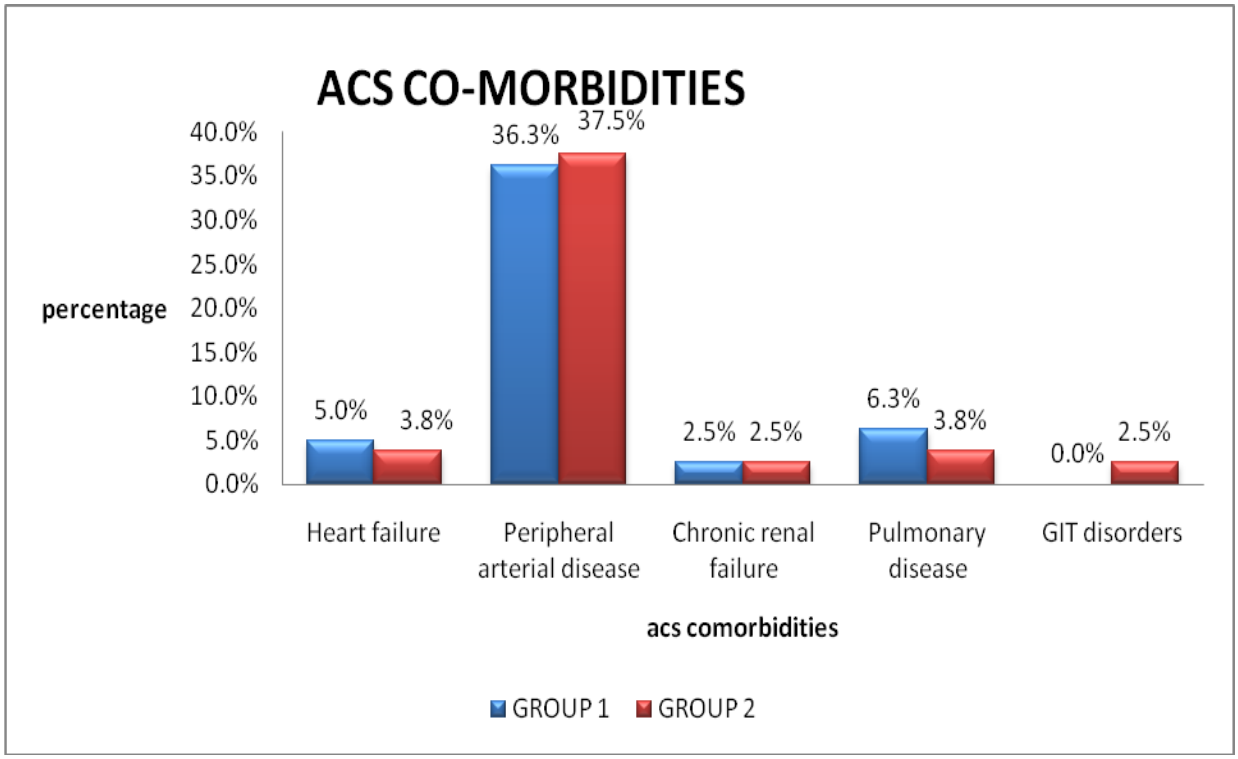


Fig.2 Etiology of ACS

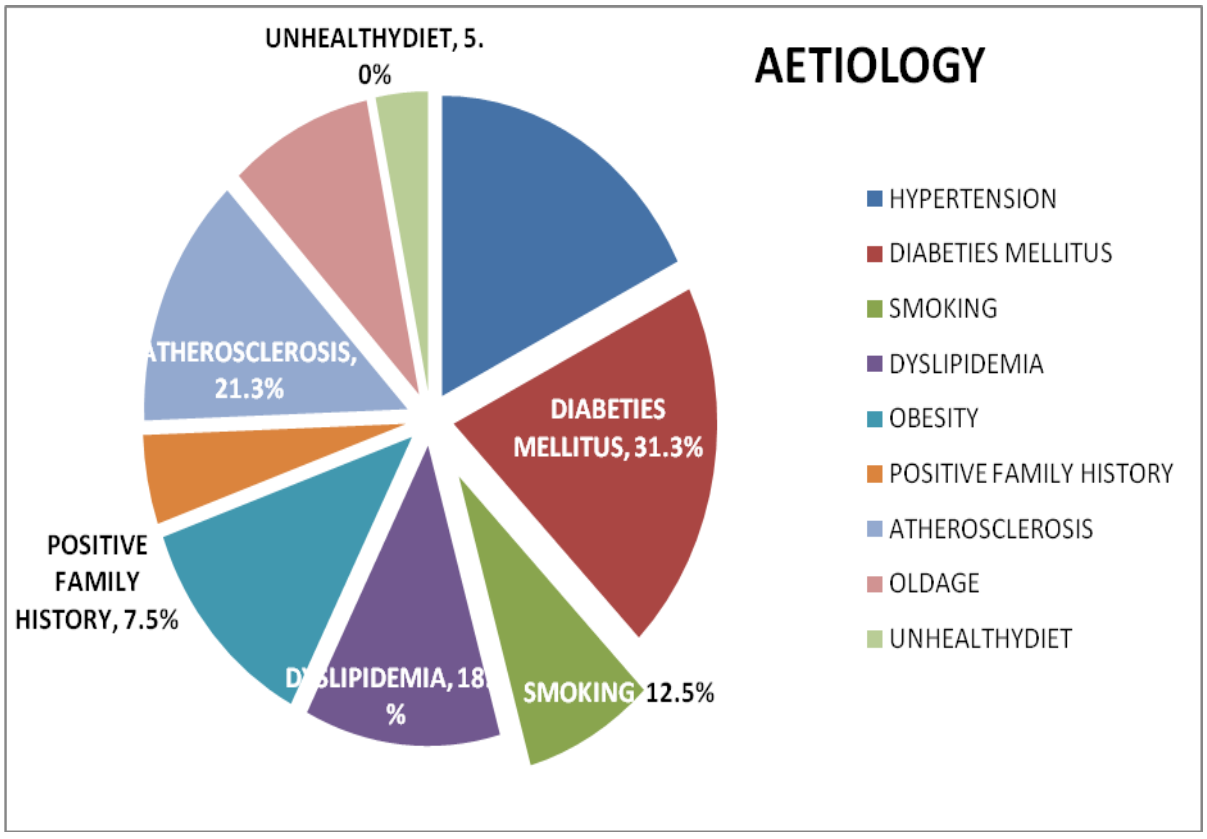


Fig.3 ADR of ACS drugs

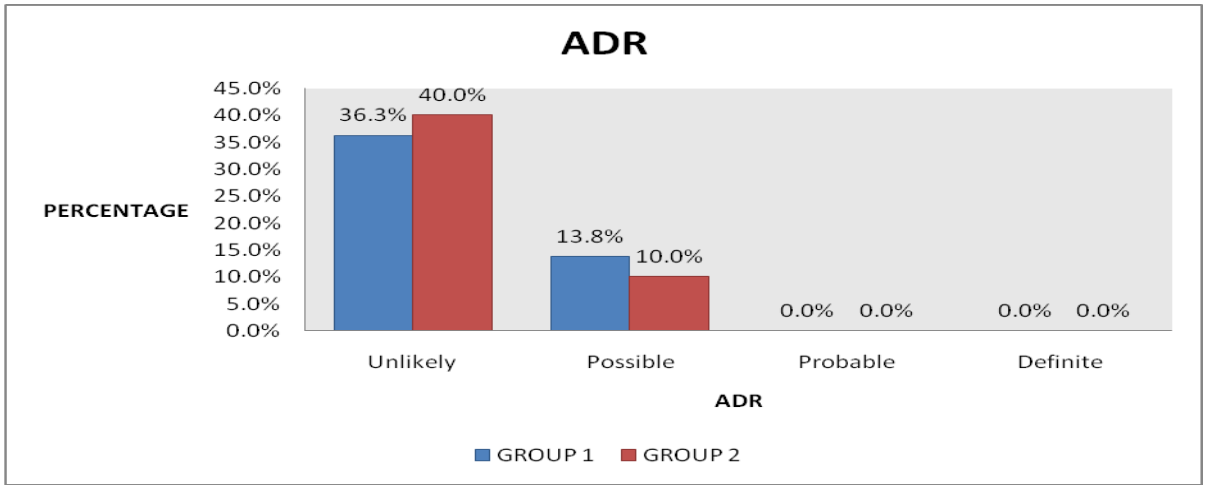


Fig.4 Medication adherence of ACS drugs

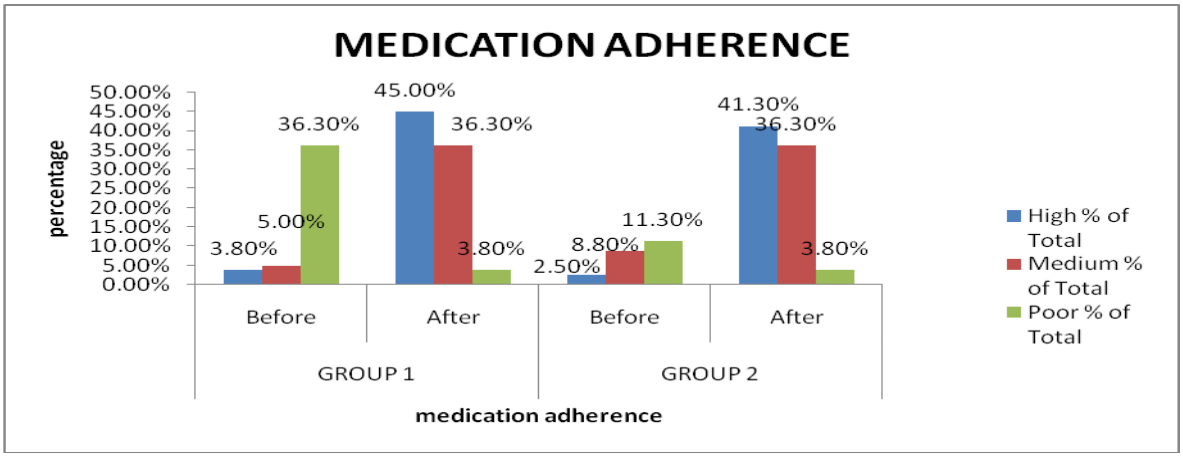
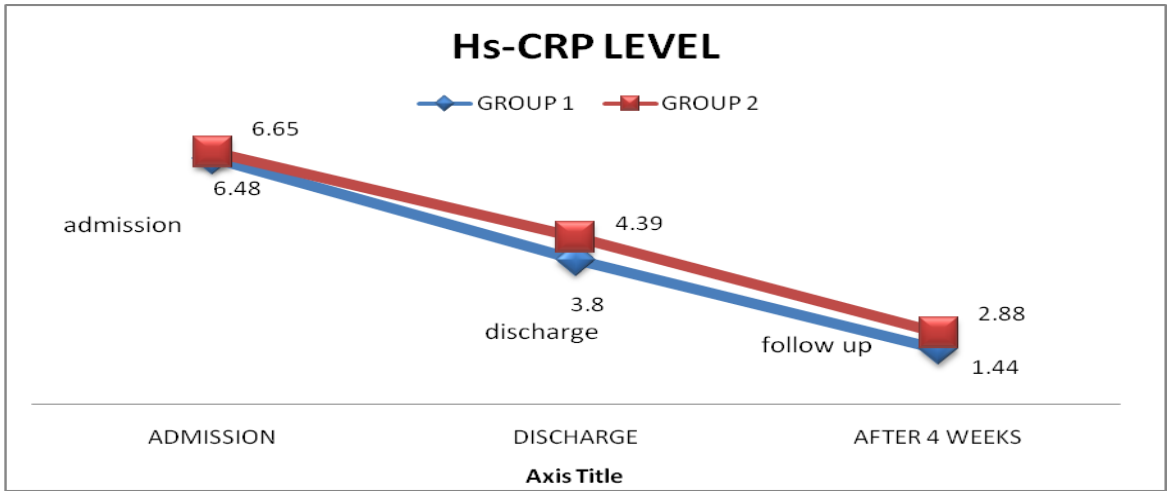


Fig.5 Effect of HS-CRP level in each groups



Since P value is less than 0.001, in both groups the level of Hs-CRP is significantly reduced. It is found to be more significant in GROUP 1.

Effect of ivabradine on hs-crp level

In the study of 80 patients, the patients was categorized into two groups, there was significant reduction of hs-CRP levels, but more significant in the group who were taking Ivabradine. Since P value was less than 0.001, in both groups the level of hs-CRP was significantly reduced. Since P>0.05 at admission there is no significant difference in the mean value of hs-CRP in both the groups. But after discharge the mean values was significantly different (P<0.05) and it was concluded that the difference is more in GROUP 1.

Ivabradine, marketed under the trade name Corlanor among others, is a medication used for the symptomatic management of stable heart related chest pain and heart failure not fully managed by beta blockers. The patients were categorized into 2 groups. Among the two groups it was observed that the hs-CRP level was significantly reduced in those who were taking Ivabradine as the p value<0.001. Ivabradine is used to reduce the heart rate by a few beats per minute in patients with the heart condition angina. Medication adherence of Ivabradine was found to be significant in patients after counselling. Blood measurements of hs-CRP were performed to assess the risk of future heart disease. It has also been suggested that hs-CRP can be used to target therapy and tailor risk modification to prevent cardiovascular disease. Administration of ivabradine reduces the hs-crp level which gradually in turn reduces the cardiovascular risk in patients. ADR was measured using narinjo scale of adverse drug reaction.ADR was found to be unlikely with most drugs.

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Conflict of interest: There is no conflict of issue with this article.

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