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RESEARCH ARTICLE

A prospective observational study on usage of inotropes in a coronary care unit

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ABSTRACT

Background: Treatment with inotropes is generally reserved for most severely ill patients and so increased mortality can be coincidental. Several clinical trials in a wide range of clinical settings have been performed with controversial results to determine the effects of inotropes on mortality. Hence, the present study was done to evaluate the effect of inotropes and vasopressors used in our setting on the outcome of the patients. **Aims and Objectives:** This study aims to assess the clinical profile of patients requiring inotropes and their outcomes in a coronary care unit. **Materials and Methods:** This prospective, observational, hospital-based study was conducted in intensive coronary care unit (ICCU). Detailed history and findings on clinical examination were recorded. Inotropes used, indication, duration of stay in hospital, various complications, and outcomes were also entered. Patients were monitored daily until their discharge or death. **Results:** The total number of patients admitted in ICCU during the study period was 199, of which 25 (12.6%) patients needed inotropes. The most common risk factor for inotrope use was diabetes mellitus (40%). The most common inotrope used was noradrenaline. The average duration of hospital stay for patients requiring inotropes was 4.7 days. Of 25 patients requiring inotropes, 64% (n = 16) survived and 36% (n = 9) expired. Chi-square test revealed that the need of inotropes was significantly associated with increased risk of death. **Conclusion:** In the coronary care unit, the use of inotropes was associated with poor outcomes. Inotropes may not be detrimental *per se*, but accurate benefits and risks and selection of the correct agent are required in every clinical setting.

KEY WORDS: Inotropes; Intensive Coronary Care Unit; Clinical Profile; Outcome; Mortality

INTRODUCTION

Inotropes are a group of drugs that are widely used in critically ill cardiac patients. The main indications of inotropes are cardiogenic shock in patients with acute coronary syndrome (ACS), decompensated heart failure, and septic shock. The major mechanism by which inotropes exhibit their efficacy in above conditions is by increasing the contractile force of heart through catecholaminergic and non-catecholaminergic pathways and thereby improving cardiac output and end-organ perfusion. The American College of Cardiology also recommends the usage of inotropes when ACS is complicated by cardiogenic shock, heart failure, and for patients with isolated right ventricular infarction with hemodynamic compromise.[1] Inotropes are also used in special situations until definitive therapy has to be decided such as heart transplantation or mechanical device implantation. In these patients, inotropes may be the only palliative therapy available till the end of the life.[2]

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Inotropic drugs enhance myocardial contractility, cause vasodilation of pulmonary and systemic blood vessels by altering peripheral arterial resistance, and can also affect the heart rate.[3] Selection of an inotrope for a patient depends on treating physician decision, center preference, and avoidance of possible adverse effects that might further deteriorate the patient's condition.[1] Adverse effects most commonly seen are arrhythmias, increased myocardial oxygen consumption, myocardial ischemia, hypotension, and metabolic alterations. Most of the commonly used inotropes exert their effects through the activation of adrenergic pathway.[4] Various studies such as randomized, observation trials and meta-analysis have shown that the use of inotropes was associated with increased mortality.[5-8] The largest database that demonstrated increased mortality with inotropes was Acute Decompensated Heart Failure National Registry (ADHERE), which showed that inotropic therapy even for a short period was associated with high rate of in-hospital mortality.[9] Furthermore, some studies have shown that the usage of inotropes during cardiac surgery has harmful effects.[10,11]

Despite there is clear evidence that inotropes increase mortality risk, they could still be the only life-saving measure available in certain clinical scenario. For example, in patients with acute systolic failure where restoration of perfusion is immediately required, intravenous inotropes have proven to have a clear therapeutic benefit. In some patients, weaning from inotropes can be difficult such that the attempts made can result in symptomatic hypotension, worsening of symptoms, and progressive end-organ dysfunction. Such patients are categorized as "Inotrope dependent." Thus, inotropes have a wide range of therapeutic benefits. Hence, it is mandatory to have a good knowledge of the pharmacology of inotropes routinely used in their institution and their indications as well as contraindications. For example, patients with ischemic cardiomyopathy with or without symptoms of angina are at substantial risk when they are exposed to inotropes.

Many strategies have been developed like mechanical devices such as intra-aortic balloon pump which are more appropriate that using noradrenaline, dopamine, or dobutamine. Many novel inotropes have also been developed which use non-catecholamine pathways such as levosimendan and milrinone with the aim of providing positive inotropic effect without enhancing myocardial oxygen consumption.[2]

Many trials on inotropes conducted in various clinical settings have provided controversial reports on mortality benefits of these drugs. In general, inotropes are reserved for patients who are critically ill rather than prophylactic use, and hence, mortality risk can be coincidental. Hence, the present study was done to describe the characteristics of critically ill cardiac patients requiring inotropic support and to determine the effects of inotropes used in our setting on the outcome of these patients.

Objectives

The objectives of the study were as follows:

- To describe the characteristics of cardiac patients requiring inotropic support in intensive coronary care unit (ICCU)
- To determine the effects of inotropes on the outcome of cardiac patients receiving inotropic support.

MATERIALS AND METHODS

Study Design

This was a prospective, observational, hospital-based study.

Study Period

The study duration was 1 month.

Study Setting

This study was conducted at ICCU, Tirunelveli Medical College Hospital.

Study Center

This was a single-centered study, Government Tirunelveli Medical College.

Study Population

Male and female patients admitted in ICCU who required inotropic support.

Inclusion Criteria

All the patients in ICCU requiring inotropic support for any indication based on decision of medical team in both sexes and age >18 years.

Exclusion Criteria

The following criteria were excluded from the study:

- Unable to provide informed consent by patient or decision-maker
- Not willing to participate in the study
- Pregnant women.

Study Procedure

The study was started after obtaining approval from Institutional ethics committee. All those who fulfilled inclusion criteria were enrolled in the study after obtaining written informed consent form patients or their legally acceptable representative and were observed during their period of stay in the ICCU. Detailed history and findings on clinical examination were recorded in a specially designed

pro forma for the study. All the investigations, procedures, inotropes used, indication, duration of stay in hospital, various complications, and outcomes were also entered in the pro forma. Patients were monitored daily until their discharge or death.

Statistical Analysis

Descriptive statistics (mean, standard deviation, range, and percentage) were used for analyzing the data. For comparison of frequency data, the Chi-square test and Fisher's exact *t*-test were used. $P \leq 0.05$ was considered statistically significant.

RESULTS

The total number of patients admitted in ICCU during the study period was 199, of which 25 (12.6%) patients needed inotropes while 174 (87.4%) patients did not need inotropes [Figure 1].

Of the 25 critically ill patients needing inotropes, 8 (32%) were female and 17 (68%) were male. Therefore, the critically ill patients needing inotropes in ICCU were predominantly male.

Table 1 shows the clinical profile of patients who required inotropes.

Premorbid conditions in critically ill patients needing inotropes in ICCU are given in Figure 2. The most common risk factor for inotrope use is diabetes mellitus (40%).

Table 2 shows the inotropes used in patients with the left ventricular (LV) dysfunction and their outcomes. The most common inotrope used was noradrenaline both as monotherapy and with other inotropes. Chi-square test of association between inotropes used and outcome of patient (Chi-square = 2.25; df = 4; $P = 0.68 > 0.05$) proved that there was no association among different types of inotropes used and outcome of patients with LV dysfunction.

The duration of treatment with inotropes and its association with outcome is shown in Table 3 which was found to be statistically insignificant.

Table 4 shows the number of inotropes required by each patient which also has no association with outcome either.

Table 5 shows the relation of outcome with the need of inotropes in patients in ICCU. Of total of 199 patients admitted in ICCU during the study period, 89% (n = 177) survived and 11% (n = 22) expired. Of 25 patients required inotropes, 64% (n = 16) survived and 36% (n = 9) expired. Among 174 patients not needed inotropes, 92% (n = 161) survived and 8% (n = 13) expired. Statistical analysis revealed that the need of inotropes was significantly associated with increased risk of death.

The average duration of hospital stay for patients requiring inotropes was 4.7 days.

DISCUSSION

The predominant patients requiring inotropes in this study were elderly males. This was contradictory to the study conducted by Chaudhury *et al*., in which females required inotropes more than males.[3] The most common risk factor in patients requiring inotropes was diabetes mellitus. Uncontrolled diabetes is the major risk factor for the development of atherosclerotic plaque and thrombosis that leads to the development of myocardial infarction (MI). Autonomic neuropathy is common in diabetic patients that predispose to infarction and is also responsible for atypical presentation of symptoms in these patients contributing to delay in diagnosis and treatment. The clinical course of MI is frequently complicated by cardiogenic shock and arrhythmia and carries a high inotropic requirement in the diabetic than in non-diabetic patients.[12] Other major risk factors associated were smoking and alcohol, and this might have contributed to the increase need of inotropes in males.

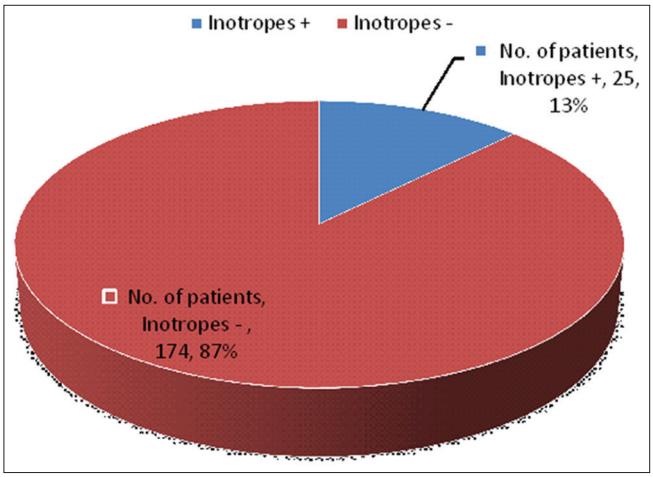

Figure 1: Percentage of critically ill patients in intensive coronary care unit who required inotropes

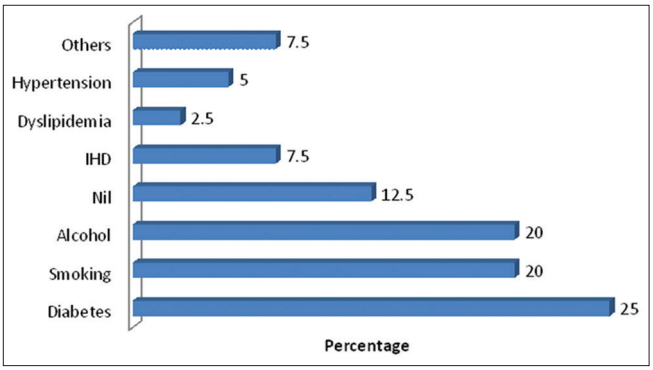

Figure 2: Premorbid conditions in patients needing inotropes

Table 1: Clinical profile of patients requiring inotropic support

Indications	Number of patients (*n*)
Coronary artery disease/acute coronary syndrome/ST-elevation myocardial infarction	29 (58)
IWMI	10 (20)
AWMI	9 (18)
Posterior wall myocardial infarction	6 (12)
LWMI	4 (8)
Unstable angina	1 (2)
Arrhythmia	9 (18)
Acute pulmonary edema	4 (8)
Cardiogenic shock	7 (14)
Suspected infarct artery	
LAD	8 (40)
RCA	9 (45)
LMCA	2 (10)
TVD	1 (5)
MI occurrence	
First	17 (85)
Second	3 (15)
Killip grade	
1	9 (45)
2	2 (10)
3	4 (20)
4	5 (25)
Intervention	
Thrombolyzed	10 (40)
Heparinized	10 (40)
PCI	1 (4)
Cardioversion/amiodarone	4 (16)
Time of admission after symptom onset	
≤6 h	9 (36)
6–24 h	11 (44)
>24 h	5 (20)
Presenting complaints	
Chest pain	22 (46)
Dyspnea	13 (27)
Palpitation	10 (21)
Syncope	3 (6)
Echo findings	
LV systolic failure	11 (44)
LV diastolic failure	3 (12)
Normal LV function	1 (4)
NA	10 (40)

Each patient had more than one defect. Among 25 patients, 20 patients were admitted for MI. LV: Left ventricular. MI: Myocardial infarction

The most common indication of inotrope use was ACS – inferior wall MI (20%) followed by anterior wall MI (18%) complicated by hypotension and hypoperfusion. The most common inotrope used in patients with the LV dysfunction was noradrenaline followed by dopamine. Dopamine and dobutamine are generally preferred when systolic blood pressure (BP) is between 70 and 110 mmHg, whereas noradrenaline is preferred when systolic BP drops below 70 mmHg. In our study, the type of inotrope used did not alter the outcome of the patients. This was in accordance

Table 2: Inotropes used for left ventricular dysfunction and their outcomes

Inotropes	Frequency (%)	Outcome	Frequency (%)
Noradrenaline	8 (32)	Survived	6 (75)
		Expired	2 (25)
Dopamine	6 (24)	Survived	5 (83)
		Expired	1 (17)
Dopamine and noradrenaline	4 (16)	Survived	2 (50)
		Expired	2 (50)
Dobutamine and noradrenaline	4 (16)	Survived	2 (50)
		Expired	2 (50)
All three	3 (12)	Survived	2 (67)
		Expired	1 (33)

*Chi-square=2.25; *P*=0.68 (>0.05) statistically insignificant

Table 3: Duration of the use of different inotropes

Duration	Frequency (%)	Outcome	Frequency (%)
≤24 h	13 (52)	Survived	8 (62)
		Expired	5 (38)
24–48 h	4 (16)	Survived	4 (100)
		Expired	0 (0)
>48 h	8 (32)	Survived	4 (50)
		Expired	4 (50)

Fisher's exact test; *P*=0.29 (>0.05) statistically insignificant

Table 4: Number of inotropes used for patients and their outcome

Number of inotropes	Frequency (%)	Outcome	Frequency (%)
1	12 (48)	Survived	9 (75)
		Expired	3 (25)
2	11 (44)	Survived	6 (55)
		Expired	5 (45)
3	2 (8)	Survived	1 (50)
		Expired	1 (50)

Fisher's exact test; *P*=0.47 (>0.05) statistically insignificant

Table 5: Relation of outcome to the need of inotropes

Outcome	Total patients *n* (%)	Survived *n* (%)	Expired *n* (%)
Inotropes needed	25 (12.6)	16 (64)	9 (36)
Inotropes not needed	174 (87.4)	161 (92)	13 (8)
Total	199	177	22

Chi-square=18.09, *P*=0.001 (<0.05) statistically significant

with the study by Chaudhury *et al*. where they did not find any association among different types of inotropes used and outcome of patients.[3] Similarly, in a study by De Backer *et al*., which compared noradrenaline to dopamine in patients with shock, both the groups did not exhibit mortality benefits. However, the patients who received dopamine had high incidence of adverse effects like cardiac arrhythmias.[13]

Dobutamine was never used as monotherapy in our study. It was always used in combination therapy only. According to flolan international randomized survival trial, dobutamine was considered as an independent predictor of mortality because 6-month mortality seen among patients who received dobutamine was high.[14] However, in our study, the use of dobutamine was not associated with increase in mortality. Long-term follow-up of patients was not done in our study.

Based on the duration of the use of inotropes, all the patients treated between 24 and 48 h survived. Within 24 h and those treated beyond 48 h, mortality was considerably high. However, the association was statistically insignificant. Mortality within 24 h can be attributed to the presence of multiple risk factors, delayed presentation, disease severity, and rapid progression of the disease. However, when the requirement of inotropes goes beyond 48 h, there may be difficult in weaning from drugs without experiencing symptomatic hypotension, recurrent congestive symptoms, or worsening renal function.[15] This leads to progressive need of inotropes. If we attempt to withdraw inotropic support in this group of patients, it can lead to life-threatening consequences.[16]

The number of patients who required combination therapy was 13 patients (52%) and those who required monotherapy were 12 patients (48%). Using the combination of agents at moderate doses may be more effective in some patients rather than using maximal doses of one medication. The outcome in monotherapy patients was good when compared to dual and triple therapy. However, the association was statistically insignificant. The number of drugs required may be more in patients with severe hemodynamic and clinical deterioration which might have contributed to the worse outcome. This is in accordance with the study conducted by Rossinen *et al*. which showed that the addition of more than one inotrope is associated with further mortality increase.[17] The number of patients who required combination therapy was 13 patients (52%) and those who required monotherapy was 12 patients (48%). Using combination of agents at moderate doses may be more effective in some patients rather than using maximal doses of one medication.

About 13% of patients who were admitted in the ICCU required inotropes in the past 1 month. Statistical analysis revealed that the need of inotropes was significantly associated with increased risk of death. The reasons may be due the fact that most of the patients who required inotropes were critically ill with rapid clinical deterioration and also the inotropic drugs might have contributed to cardiac compromise when multiple agents with increasing doses

were used. The ADHERE trial showed that patients who received short-term vasodilator therapy had significantly lower in-hospital mortality than patients who received inotropic therapy.[9] Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure trial also showed that heart failure patients in intravenous inotrope had increased morbidity associated with hypotension and new atrial arrhythmias.[18] The results of the present study are also in accordance with another study which observed that inotropes following cardiopulmonary bypass were associated with higher 30-day mortality.[19] Furthermore, a recent analysis of data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial showed that 6-month mortality risk in decompensated heart failure patients who received an IV inotropic agent was increased by 1.8-fold times than patients who did not receive inotropic drugs.[20] Although so many trials supported our finding, this recent meta-analysis showed that the use of inotropes was not associated with mortality risk. However, in the limitation, they have mentioned that the survival benefits attributed to inotropes might be influenced by articles involving levosimendan therapy which acts by non-catecholamine pathway and have a clear benefit in survival rate. This drug is not being used in our set up.[4]

Limitations

The first limitation was being an observational study. Second, the sample size was small. Third, long-term follow-up of patients after discharge was not done. Fourth, only the effects of inotropes acting through adrenergic and dopaminergic receptors were studied. Inotropes acting through non-catecholamine pathway were not used in our institution.

CONCLUSION

In the coronary care unit, the use of inotropes acting through catecholaminergic pathway was associated with poor outcomes in some patients. These inotropes are not dangerous by themselves. Always benefits and risks should be outweighed and selection of appropriate inotrope should be individualized. Newer inotropes acting through non-catecholamine pathway can be introduced.

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