

## **Title: COMPARISON OF THE EFFICACY OF $\beta$ BLOCKER AND IVABRADINE IN POST COVID-19 ASSOCIATED INAPPROPRIATE SINUS TACHYCARDIA.**

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### **Abstract:**

**Introduction:** Covid 19 infection is a recent pandemic which has been linked numerous symptoms post recovery from acute illness. Inappropriate sinus tachycardia [IST] is one of the conditions seen in patients recovered from Covid 19 infection. Currently there is no effective treatment for IST. The present study compares the efficacy of Beta blockers and Ivabradine in controlling the heart rate in IST.

**Methods:** A multi centric prospective study was carried out in 48 patients who developed Post COVID IST for a period of six months. The data was collected and analysed using appropriate statistical test for comparison of minimal, mean, and maximum heart rate at zero, three, and six months.

**Results:** The participants were divided into two random groups. Group A received Metoprolol 50 mg once daily and group B received Ivabradine 5 mg twice daily. Both the groups were followed and then their minimal, mean and maximal heart rate was recorded at zero, three and six months. Both the drugs were found to be effective in decreasing the heart rate with a *p* value of less than 0.05. Ivabradine was found to be superior than metoprolol in controlling mean heart rate over six months duration with a *p* value of less than 0.01. Ivabradine also had better effect than metoprolol in controlling maximal heart rate at three months with a *p* value of less than 0.01 and over six months with a *p* value of less than 0.001.

**Conclusion:** Treatment of post COVID 19 IST with Ivabradine has shown to improve basal as well as mean heart rate and is more effective than Beta blocker for a long term use. It can be used as a better alternative to Beta blocker who developed its side effects or are intolerant to it.

**Keywords:** Inappropriate Sinus Tachycardia , Ivabradine , Beta blocker , Metoprolol , COVID 19.

**Introduction:** The most recent viral infection caused by acute respiratory syndrome corona virus 2 (SARS-CoV-2) is responsible for the pandemic of the corona virus disease 2019 (COVID-19). As per WHO statistics, by the end of 2021, there have been 27,64,36,619 confirmed cases of COVID-19, including 53,74,744 deaths.<sup>1</sup> Even though the patients are recovering from the acute phase of Covid-19 infection, but the convalescence phase is lasting for more than 3 months in majority of the patients. During this phase, the patients experience variety of symptoms like fatigue, chest pain, reduced exercise tolerance, dyspnoea, fever, headache and palpitations.<sup>2</sup> Inappropriate sinus tachycardia (IST) is a diagnosis of exclusion, where identifiable causes of sinus tachycardia has been excluded.<sup>3</sup> It is associated with increase in heart rate without any physiological stimulus. If it takes a chronic course, it can have adverse effect on the quality of the life. Currently, there is no effective treatment for IST. Beta blockers are most commonly used but are poorly tolerated and often ineffective.<sup>4</sup> Ivabradine is a sinus node inhibitor which also decreases the heart rate. The current study was done to determine the appropriate treatment of inappropriate sinus tachycardia observed in patients recovered from Covid-19 and to compare the efficacy of beta blockers and ivabradine in decreasing the heart rate in IST.

**Methods:** A multicentric prospective study was carried out for the duration of 6 months starting from February 2021 to July 2021 in 48 patients who developed inappropriate sinus tachycardia following recovery from Covid 19.

Inclusion criteria:

1. Post-covid patients developing inappropriate sinus tachycardia
2. Age >25 years and <60 years.
3. Resting ECG showing HR >100 bpm or Medium Holter ECR HR > 90 bpm.

Exclusion criteria:

1. Patients with arrhythmias other than tachycardia
2. Hypertensive patients
3. Patients on beta blockers or any other rate lowering drugs.
4. Patients with known cause of tachycardia like hyperthyroidism, anaemia, fever etc.
5. Patients with Heart failure or structural heart disease.

6. Patients with postural orthostatic tachycardia syndrome.

7. Patients with sinus nodal re-entrant tachycardia.

All the patients included in the study were subjected to a variety of tests to rule out known causes of tachycardia like hyperthyroidism, fever, anaemia, anxiety, electrolyte imbalances or lung pathology. Complete drug history and personal history was taken to rule out any of these as a cause of tachycardia. After undergoing the preliminary screening, the patients were labelled as suffering from post covid inappropriate sinus tachycardia and were included in the study. Informed consent was taken for inclusion in the study. These patients underwent comprehensive tests like 2d Echo, 24 hours Holter monitoring, 6minute walk test and blood tests for the myocardial inflammation and damage. The patients were randomly divided into two groups, irrespective of age and sex. First group received a beta blocker while the other group received Ivabradine. Patients were followed up for the change in the heart rate, resolution of the symptoms or development of any adverse effects. The data was collected and spread on the Microsoft excel Sheet and analysed using SSPS version 20.

### Results:

In the present study 48 patients of inappropriate sinus tachycardia were included out of which 26 were males and 22 were females. All the patients had a history of COVID 19. Average age of the participants was  $40.7 \pm 12.0$ . The participants were divided randomly into two groups group A and B. Group A received Metoprolol 50 mg once daily initially titrated to maximum of 100mg once daily. Group B received Ivabradine 5 mg twice daily increased to maximum of 7.5 mg twice daily, if the symptoms persist or basal heart rate was persistently high. Age and Gender wise distribution is depicted in Table 1 and Table 2.

Table 1: Distribution of participants according to Gender:

	GROUP A	GROUP B
MALE	14	12
FEMALE	10	12
TOTAL	24	24

Table 2: Age Distribution of participants:

	GROUP A	GROUP B
MALE	$45.1 \pm 12.29$	$46.0 \pm 13.31$
FEMALE	$37.1 \pm 8.78$	$36.8 \pm 10.48$

At the start of the study, the minimal heart rate, mean heart rate and maximal heart rate of all the participants was recorded. It is summarized in Table 3.

Table 3: Minimal, Mean and Maximal Heart rate of the participants at 0 months of study.

0 MONTHS	GROUP A	GROUP B
MINIMAL HEART RATE	$100.35 \pm 14.45$	$96.32 \pm 11.46$
MEAN HEART RATE	$113.10 \pm 10.70$	$111.73 \pm 9.62$
MAXIMAL HEART RATE	$132.25 \pm 12.64$	$135.26 \pm 13.1$

After enrolling in the study, participants of both the groups were followed up and their minimal, mean and maximal heart rate was recorded after 3 months and 6 months of treatment with Metoprolol in Group A and Ivabradine in Group B. The results are summarized in table 4 and Table 5.

Table 4: Minimal, Mean and Maximal Heart rate of the participants after 3 months of treatment.

3 MONTHS	GROUP A	GROUP B
MINIMAL HEART RATE	92.95± 12.3	89.63±7.8
MEAN HEART RATE	100.64± 11.24	94.38±8.62
MAXIMAL HEART RATE	118.64± 13.03	111.47±9.2

Table 5: Minimal, Mean and Maximal Heart rate of the participants after 6 months of treatment.

6 MONTHS	GROUP A	GROUP B
MINIMAL HEART RATE	87.39± 9.82	82.47±6.46
MEAN HEART RATE	94.16±9.7	88.97±4.99
MAXIMAL HEART RATE	109.56± 10.91	96.32±8.17

After 6 months of treatment, Group A and Group B were compared with regards of changes in the minimal, mean and maximal heart rate. The results are depicted in Table 6. It is seen that both Metoprolol and Ivabradine were affective in decreasing the heart rate with a p value of <0.05. Ivabradine proved to be superior to Metoprolol in controlling Mean heart rate over 6 months duration with a p value of <0.01. Ivabradine also had better effect than metoprolol in controlling the maximal heart rate at 3 months with a p value <0.01 and over 6 months with a p value <0.001.

	P VALUE	GROUP A	GROUP B
MINIMAL HR	0 VS 3	<0.05	<0.05
	3 VS 6	<0.05	<0.05
	0 VS 6	<0.05	<0.05
MEAN HR	0 VS 3	<0.05	<0.05
	3 VS 6	<0.05	<0.05
	0 VS 6	<0.05	<0.01
MAXIMAL HR	0 VS 3	<0.05	<0.01
	3 VS 6	<0.05	<0.02
	0 VS 6	<0.01	<0.001

**Discussion:** Inappropriate sinus tachycardia is a condition that is characterised by increase in heart rate >100 beats per minute without any underlying cardiac abnormality or any other systemic pathology. IST is one of the common complications seen in patients recovered from Covid 19, especially the younger individuals.<sup>5</sup>The most commonly used medications used for the treatment of IST are the beta blockers and the calcium channel blockers. But in general,

they are not tolerated at the doses required to control the heart rate.<sup>6</sup>In the present study, it is observed that patients responded well to Ivabradine when compared to the beta blockers.Ivabradine is a unique drug that can lower the heart rate without significant side effects commonly seen with the similar medications.<sup>7</sup>Ivabradine blocks the intracellular part of the pacemaker or “funny” current (If) transmembrane channel.<sup>8</sup> It does so by selectively inhibiting the cation movement leading to decrease in the slope of the action potential, eventually resulting in slowing the heart rate. The action of Ivabradine is dose dependant as it blocks the channel in its open state, therefore it becomes more potent at faster heart rates. Because of this specific mechanism of action, it is able to do decrease the heart rate without affecting cardiac inotropy or systemic vascular resistance.<sup>9,10</sup>

A prospective, single-centre study was conducted by Ptaszynski Pet al on 20 patients with IST in whom treatment with ivabradine was compared with slow-release metoprolol. Both drugs had highly significant and comparable effects on resting and Holter-based heart rate. Ivabradine overpowered metoprolol in the reduction of mean heart rate during daily activities and in the reduction of symptomatic episodes during 24-h Holter monitoring.<sup>11</sup> Similarly a study conducted by Annamaria M et al showed that Ivabradine is effective and safe in short and medium term treatment of IST. However, long-term follow-up studies and randomized studies comparing ivabradine with beta blockers are still lacking.<sup>12</sup> In a prospective randomised controlled study conducted by Cappato et al, Ivabradine significantly improved symptoms associated with inappropriate sinus tachycardia and completely eliminated them in approximately half of the patients.<sup>13</sup> A similar study conducted by Zellerhoff S has also shown that Ivabradine appears effective and safe in patients with symptomatic inappropriate sinus tachycardia.<sup>14</sup> When compared to Calcium calcium blockers and beta blockers for treatment of IST, Ivabradine could be used as a safe alternative as per Calo L.

In contrast to the above, an article published by K. Kaczmarek showed that almost all patients with excessive sinus node automaticity were asymptomatic on treatment but the majority of patients with autonomic dysregulation reported residual symptoms.<sup>16</sup> There is no evidence of ivabradine influence on autonomic nervous system the sinus rate decrease may be assigned to the effector suppression. A meta analysis on Ivabradine has shown that Ivabardine is associated with 15% increased risk of developing Atrial fibrillation, which can be a major factor restricting its use in IST, which is a relatively benign condition.<sup>17</sup>

Thus, It can be seen that Ivabradine may be safe alternative in treatment of IST due to Covid 19. However, there are some limitations in the present study like short duration of study time and small number of study participants. It requires more extensive and large trials to establish the safety and efficacy of Ivabradine use in such patients.

#### **CONCLUSION:**

Inappropriate Sinus Tachycardia is common after Covid 19 infection and Treatment with Ivabradine has shown to improve basal as well as mean Heart rate. It is effective in decreasing the symptoms of the such patients. Thus, It can be considered as effective as  $\beta$  blockers and calcium channel blockers. It can also be used as a safer and effective alternative in patients who develop side effects or intolerance to these generally prescribed rate control medications.

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