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Comparison of Conventional Beta-Blockers and A New Pioneer, Mavacamten (MYK-461): A Cardiac Myosin Modulator, in Management of Hypertrophic Obstructive Cardiomyopathy

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Introduction

Cardiovascular disease (CVD), is one of the leading causes of global morbidity and mortality. It is most commonly associated with Hypertrophic obstructive cardiomyopathy (HOCM) [1]. The incidence of HOCM is 1:500 in the adult population [2,3]. According to a study conducted in 2016-2018, 2.7% of males and 1.6% of females are having HOCM. The incidence of HOCM is increasing with advancing age, as 0.36/per 10,000 people under the age of 18 and 4.28 per 10,000 persons the age of 55-64 years [4]. HOCMs are mainly autosomal dominant but metabolic storage diseases and neuromuscular diseases also account for its development [5]. Mutations in one of the genes encoding cardiac sarcomere, Z-disc, and calcium-controlling proteins are linked to HOCM development. Twenty genes have been identified so far, however, the two most often mutated genes are myosin-binding protein C and -myosin heavy chain (MYH7) (MYBPC3) [6,7]. HOCM is the primary non-ischemic disease, considered to be one of the major factors for sudden cardiac failure and death [2]. HOCM is characterized by an enlarged left ventricle, hyperdynamic contraction, and poor relaxation due to abundant cardiac-actin and myosin interactions [1,8]. Left ventricular hypertrophy includes, septal hypertrophy that causes high left ventricular outflow tract, which in turn leads to suction effect and traction of mitral valve cusps towards the anterior interventricular septum. This traction consequently produces sub-aortic systolic gradient and left ventricular outflow tract obstruction (LVOTO) [6]. A ventricular gradient larger than 30 mmHg is referred to as LVOTO, which remains symptomless unless 50mmHg. At rest, it affects 25% of individuals with hypertrophic cardiomyopathies and can worsen in 30% of patients during activity (dynamic LVOTO) [9,10]. Myocardial hypertrophy or systolic anterior movement (SAM) of the mitral valve (MV) leaflet are the two factors that contribute to obstruction. Symptoms associated with HOCM include dyspnea, chest pain and syncope, resulting in major concerns for one's life [1,5, and 11].

The management of HOCM can be pharmacological or interventional. Pharmacological measures have been used since past many years as the recommended old standard guidelines. These included Beta-blockers, non-dihydropyridine calcium channel blockers [1,12]. In non-responsive patients to the above therapy, disopyramide is usually administered.1 Beta-blockers are considered to be the first line of management, unless contra-indicated. Beta-blockers decrease the heart rate and improve the ejection fraction [13]. Contraindications include asthma, hypoglycemia, and the administration in a person on antiarrhythmic drugs [14]. The side effects associated with all of the diseases are least tolerable compared to the efficacy, so inclination towards the surgical intervention of septal reduction is considered. Unfortunately, no prospective data on post-surgical intervention is available that can modulate the perspective of pharmacological superiority [15]. Recently, a reversible, selective inhibitor of cardiac myosin ATPase, mavacamten (MYK-461), has been introduced.1 According to New York Heart Association, class II and III adult patients of HOCM, with symptomatic heart failure, are legible for MYK-461 use [16]. This drug decreases the actin-myosin cross-bridges, so demolishing the likelihood of systolic and diastolic cross-bridging, which is the hallmark of HOCM [16,17]. MYK-461 reduces the LVOT obstruction, hence increasing the cardiac filling pressure. IT selectively reduces cardiac contractility by restoring the normal ratio of myosin heads to a relaxed state [17,18]. This drug has a half-life of 8 days with 85% bioavailability [16,19]. This drug is under consideration for many clinical trials and has provided efficient results compared to conventional pharmacological measurements, as discussed in the results. Keeping in mind the escalating rise in HOCM with advancing age, particularly in developing countries, there is an urgent need of deciding the efficient management plans, with fewer adverse effects.

Aim of this study is to compare the efficacy, side effects and prognosis of two different drugs for HOCM, the conventional beta-blockers and Mavacamten, a novel myosin inhibitor.

The rational of this review is to compare Mavacamten and beta blockers in HOCM to help clinicians in deciding the best management plan, and if found significant, incorporate them in departmental protocol to decrease the global burden of this disease.

Methodology

This systematic review was started in May 2022 under the heading of "Comparison of Conventional Beta-Blockers and A New Pioneer, Mavacamten (MYK-461): A Cardiac Myosin Modulator, in Management of Hypertrophic Obstructive Cardiomyopathy".

Duration

May 2022 till September 2022.

We included articles from September 2017-August 2022. Total 41 articles were obtained. Out of which only 12 were selected discussing the exclusive use of Mavacamten and beta-blockers in patients of HOCM.

Data selection

Quantitative or qualitative studies, particularly clinical trials on Mavacamten administration in patients of HOCM, and conventional pharmaceutical management of HOCM patients with beta-blockers, were included. Significant data was collected from the Web of sciences, SCOPUS, Medline, PubMed and WHO EMRO.

Inclusion criteria

1. Studies including Mavacamten administration in HOCM patients.

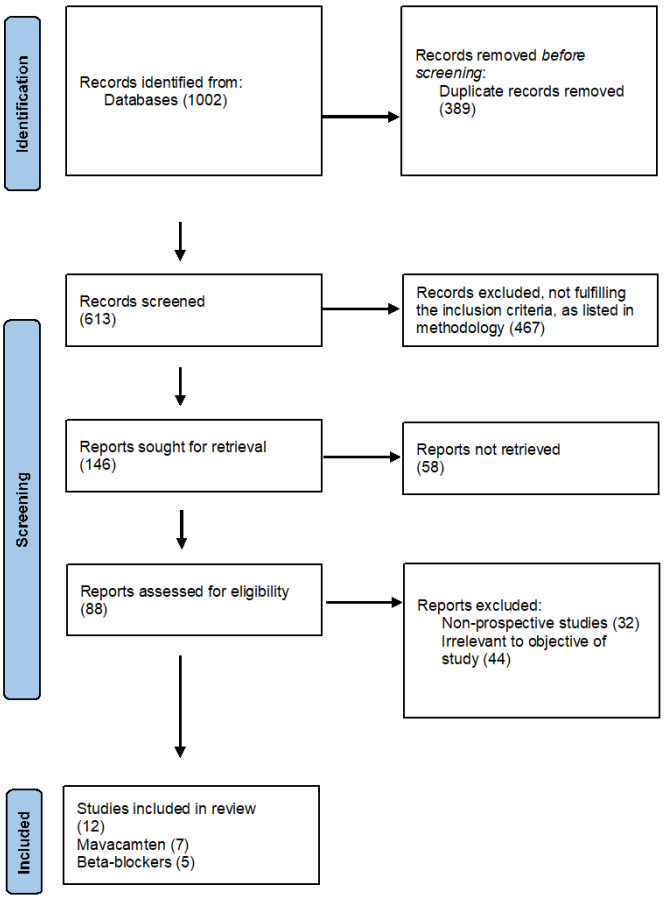
2. Studies providing data for administration of Beta blockers as conventional management plan.

Exclusion criteria

1. Studies involving patients with ailments that can predispose to early development of HOCM.

2. Studies involving patients, who were already on Beta-blockers but later switched to Mavacamten.

3. Studies involving any pharmacological management of HOCM, other than Mavacamten and Beta-Blockers.



Protocol: Identification of studies via databases and registers.

Table 1: Mavacamten administration with outcomes in management of HOCM.

Sr.#	Study	No. of patients	Dosage	Outcome
1.	Heitner SB, et al. (2019) [18] NCT02842242	21	Mavacamten 10-15 mg for 12 weeks	reduction of peak exercise LVOT gradient by 90 mm Hg in 08/11 subjects, while 3 suffered from decreased LVEF with recovery.
2.	Olivotto I, et al. (2020) [20] NCT02842242	251	Mavacamten 2.5-15 mg 30 weeks	Improved exercise capacity, LVEF to ≤50% in 7 patients and with recovery of LVEF in all.
3.	Maron BJ, et al. (2022) [21]	Not mentioned. But 43% had significant outcome	Not mentioned.	7 patients in EXPLORER-HCM (5.6%) also developed systolic dysfunction (ejection fraction) <50%. patients including up to a 57% from baseline, though reversible on drug cessation (92% to 35%).
4.	Ho CY, et al. (2020) [22]	-	350 to 700 ng/mL plasma concentration for 12 weeks	Mavacamten causes a dose-dependent reduction in LVEF.
5.	Saberi S, et al. (2021) [23]	17	For 30 weeks	Decreased Left ventricle mass, raised Left ventricular Ejection fraction.
6.	Desai MY, et al. (2021) [24]	100	16 weeks	Significantly demolishes the need of Septal Reduction Therapies in HOCM patients.
7.	Spertus JA, et al. (2021) [1]	429, 123 received Mavacamten	5mg, for 30 weeks	Improved exercise capacity, LVOT obstruction.

Table 2: Beta-blockers administration with outcomes in management of HOCM.

Sr.#	study	No. of Patients	Dosage	Outcomes
1.	Javidgonbadi D, et al. (2019) [25]	121	125mg/day metoprolol	Early beta blocker therapy improved survival rate, but not much effective for resting obstruction. Only significant for exercise induced stress.
2.	Sanchez-Nadales A, et al. (2019) [26]	Case report	Beta-blocker intake history.	Symptoms of LVOT obstruction still persists. This can be due to usage of less adequate dosage.
3.	Dybro AM, et al. (2021) [27]	29	For 2 weeks	LVOT gradient during metoprolol was lower at rest.
4.	NCT03532802	30	50-150mg, up filtration done in 1st week then steady state in 2nd week.	Not mentioned.
5.	Anthony A, et al. (2021) [31]	29	6 weeks	Decreased LVOT gradient but no effect on exercise capacity.

4. Studies on post-surgical (myectomy) administration of any of the concerned drugs of study.

Study Protocol

A systemic review was conducted according to the Cochrane handbook of systemic reviews and reported based on PRISMA.

Results

Discussion

In the recent past, scientific innovation and aspiration have improved management plans of hypertrophic obstructive cardiomyopathy. This insight has transitioned the first-line treatment plan towards pharmaceutical management for LVOT obstruction, rather interventional. According to the current research, conventional beta blockers and novel Mavacamten are the key therapies. They relieve LVOT obstruction and its associated symptoms. The hemodynamics (LV diastolic filling) and heart failure symptoms are also addressed by medications. Beta-blockers are an evidence-based therapy for HOCM at rest, for decades. They reduce LVOT obstruction, angina, dyspnea on exertion & ventricular arrhythmias by reducing the heart rate, increasing the time of diastole & reducing ventricular [14,25-28]. These effects have been particularly predominant in the resting state. So, with the advancement of science and the need for non-resting state therapy for HOCM, there must be an establishment of novel agents that lower the HOCM morbidity and its associated mortality. The dosage of beta blockers can be adjusted according to the patient's symptoms and tolerance. Among the most frequent side effects associated with beta-blockers, are exhaustion and a decrease in libido. Some individuals also experience sleeplessness, altered sleep patterns, and nightmares. When beta blockers cross the blood-brain barrier, this effect is more pronounced. While taking beta-blockers, some people may feel lethargic or gain weight. This drug must be stopped to manage these side effects. Beta-blockers are contra indicated in patients with Reynold's phenomenon [29,30].

One important factor affecting cardiac contractility is the controlled activation of the cardiac myosin thick filament, which influence the Frank- Starling law, a pillar of cardiac performance. Mavacamten is a cardiac myosin ATPase inhibitor. It keeps the energy expenditure for cardiac contractility low, hence providing energy for myocyte utilization. During actin deficiency, the free energy required to open the pathways that release phosphate and bind nucleotides, which respectively limit phosphate and ADP release, increases [31]. According to a study by Olivotto I, et al. (2020) [20], at the end of 12 weeks, Mavacamten lowered the mean post-exercise LVOT gradient from 103 mm Hg (SD, 50) at baseline to 19 mm Hg (SD, 13) (mean change, -89.5 mm Hg [95% CI, -138.3 to -40.7 mm Hg]; P = 0.008). LVEF during rest was similarly decreased [20]. Another study by Saberi S, et al. (2021) [23] proposed, Mavacamten caused an LVEF drop in the EXPLORER-HCM population that was comparable to that measured by echocardiography in the CMR sub-study (6.6% [6.39%] and -3.9% [7.7%]). By CMR, there was no LVEF below 50%. The CMR sub-study included two individuals (1 mavacamten, 1 placebo), both of whom were asymptomatic at the time of the measure, out of the nine patients in EXPLORER-HCM (7 mavacamten, 2 placebo) with a transient drop in LVEF 50% (median 48%) by echocardiogram. Another measure of LV systolic function, a

myocardial contractile fraction (MCF=(LVSV/LV myocardial volume) x100, LV myocardial volume=LV mass/1.05 g/mL), was similar in both groups at baseline (mavacamten: 61.0% [17.9%], placebo: 60.1% [17.3%]), and remained unchanged at week 30 [23].

Researches has proposed Mavacamten as a novel therapeutic agent for HOCM due its significant effect on lowering the LVOT obstruction despite the level of activity. Though some researches have also shown a decrease in Left ventricular ejection fraction, but it remains reversible. So, by administering the optimal dosage of Mavacamten, the detrimental effects associated with LVOT obstruction can be prevented [18-24].

Conclusion

Beta-blockers have been a mainstay treatment for ages and they still are under resting basal conditions for HOCM but a novel therapeutic agent, Mavacamten has also shown a ray of light for exercising HOCM. Though there is still a need for more clinical trials based upon different ages, race, gender and pre-post exercise, to help in achieving non-hazardous pharmacological management for HOCM.

Limitations of Study

The only limitation of the study was non-access to some of the clinical trial-based articles on Mavacamten and Beta-blockers therapy.

Conflict of Interest

The Authors declare no conflict of Interest.

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