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Original Research Paper

Ayurveda

IMPACT OF ISCHEMIA REVERSAL PROGRAM ON THE TIME TO ONSET OF ISCHEMIA IN PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE.

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ABSTRACT Chronic ischemic heart disease (IHD) is a cardiovascular disease that results in an imbalance between the myocardial oxygen demand and supply. Despite several advances in medical science leading to a better understanding and management of IHD, this disease continues to be one of the worldwide leading causes of mortality. This necessitates the development of supplementary alternatives for the management of chronic IHD. This retrospective study evaluates the effectiveness of an ischemia reversal program by exploring its impact on the time to onset of ischemia through an evaluation of primary endpoints (maximum oxygen uptake capacity [VO2 max] with the resultant metabolic equivalents of task [METs] and Duke Treadmill score [DTS]) and secondary endpoints [body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and body weight] in patients with chronic IHD. Significant improvements in these primary and secondary endpoints indicated that the application of ischemia reversal program can delay the onset of ischemia and result in an improvement in the overall quality of life.

KEYWORDS : Ischemic Heart Disease, VO2 max, MET, Duke treadmill Score, Body mass index, blood pressure.

INTRODUCTION:

Chronic ischemic heart disease (IHD) is a cardiovascular disease that results in a transient mismatch between the myocardial oxygen demand and supply that in turn can lead to reversible myocardial ischemia.[1] The condition is diagnosed and a risk stratification of the disease is undertaken using an ECG exercise stress test.[2] If left untreated, chronic IHD may eventually lead to severe heart damage resulting in life threatening acute symptoms, including heart failure. The management of chronic IHD aims to reduce existing symptoms by prescribing anti-anginal drugs[3] and improve prognosis through a reduction in the burden of coronary risk[4] and administration of antiplatelet agents[5].

In India, the burden of IHD is immense. According to the Registrar General of India, within a decade the percentage of total deaths due to IHD increased from 17% (in 20012003) to 23% (in 2010-2013).[6] During the same duration, the percentage of adult deaths occurring due to IHD, increased from 26% (in 2001-2003) to 32% (in 2010-2013). Rapid industrialization and urbanization that contributes to an increase in stress, modifications in the dietary habits of individuals due to wider food choices, and the adoption of an increasingly lethargic lifestyle are the major reasons for this epidemiological transition observed in India.

The regular use of conventional allopathic medications such as beta blockers, calcium channel blockers, nitrates, acetylsalicylic acid, and statins is a significant factor for controlling chronic IHD. However, these medications not only increase the cost of administering healthcare but more importantly also expose a patient to undesirable long term adverse events of these drugs that, in turn, can lead to decreased compliance. As a result, there is an urgent need to promote secondary prevention approaches that complement the primary approaches currently in practice to control chronic IHD and thereby improve the overall quality of life in patients suffering from this condition.

Supplementary alternatives for management of IHD often include cardiac rehabilitation programs that contribute towards improving physical endurance and quality of life and preventing complications. Practicing such supplementary programs does not interfere with the administration of prescribed allopathic medications. However, the rewards of practicing these can lead to an overall dosage reduction of the prescribed allopathic medications that in turn can prevent or prolong the advent of long-term adverse events.

Ayurveda Based Ischemia Reversal Program: The administered Ayurveda based ischemia reversal program is a combination of Panchakarma and allied therapies. Ischemia reversal program is specifically designed to correct the imbalance between demand and supply of myocardial blood flow. This program is proposed to be an add on therapeutic regimen that can be easily coupled with any other ongoing treatment regimen.

Ischemia reversal program involves a 3-step procedure that takes about 65-75 minutes and is performed on patients with IHD after a light breakfast using a variety of decoctions and oils described ahead:

a. **Snehana/external oleation or massage:** This is a 30-35-minute procedure that involves the administration of an external massage to IHD patients using an oil-based decoction. The massage technique uses centripetal or upward strokes directed towards the heart. This procedure aims at increasing the venous return.
b. **Swedana/passive heat therapy:** This is a 10-20-minute procedure that is administered to IHD patients while lying inside a sudation box, in a supine position, with their head positioned outside the box. The treatment involves steadily passing steam containing a group of ten herbs (Dashmoola) at a maximum temperature of 40 C for 10-15 minutes. After the treatment, patients are suggested to relax for 3-4 minutes. This procedure is aimed at improving the local blood supply through vasodilation.
c. **Basti/per rectal drug administration:** This is a 15-minute procedure that involves the per rectal administration of drugs (*Tribulus terrestris*, *Curcuma longa*, and *Emblica*

officinalis) to IHD patients. These drugs remain inside the body for =15 minutes to ensure maximum absorption and help in the release of nitric oxide from vascular endothelium. The nitric oxide released acts through coronary vasodilation, antiinflammatory action, and antioxidant action.

With a combined effect of increased venous return and improved vasodilation, ischemia reversal program is expected to provide an improved supply of oxygen to the heart thereby delaying the time to onset of ischemia. The delay in the time to onset of ischemia can be monitored through an improvement in maximum oxygen uptake capacity (VO 2 max)[7], the resultant metabolic equivalents of task (MET)[8], and the Duke treadmill score (DTS)[9] as the primary endpoints and through a measurement of secondary endpoints such as body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and weight control. The objective of this present observational study was to evaluate the impact of ischemia reversal program on the time to onset of ischemia through an evaluation of these primary and secondary endpoints in ischemia patients.

MATERIALS AND METHODS:

This was a retrospective observational study conducted between April 2019 to September 2019. The study used data of patients with IHD who were assessed for the presence of inducible cardiac ischemia using exercise treadmill testing. All patients provided a written informed consent towards publishing the data generated out of this study. Adult male or female patients with a minimum age of 18 years were considered for this study. These patients had attended the out-patient departments (OPDs) of various clinics located across Maharashtra, India. The patient data considered for this study included patients who had been administered the ischemia reversal program over a period of 90 days (±15 days) and who underwent a minimum of 7 sittings. The inclusion of patient data files for this retrospective analysis, was based on the availability of complete relevant baseline data (on Day 1 of the ischemia reversal program) and final day data (on Day 90 of the ischemia reversal program).

Of a total of 524 data files screened for availability of complete data, 208 patient files were selected and their data were considered for analysis. The present study involved a total of 208 IHD patients with a mean age of 59.39±10.33 years. The age of the patients included in this study ranged from 26 to 84 years of age. Majority of the patients were males (138 [66.34%] patients) as compared to females (70 [33.65%] patients).

On Day 1 of the ischemia reversal program, all 208 patients underwent VO 2 max, Duke treadmill scoring, SBP, DBP, weight, and BMI measurements per the international recommendations. The time for which a patient could exercise during the Duke treadmill test, until the observation of a 1 mm deviation (depression or elevation) of the STsegment from the isoelectric line, was recorded as the time to onset of ischemia. These readings were considered as baseline readings. Additionally, the metabolic equivalents of task (METs) value was calculated by dividing the oxygen uptake indicated via VO 2 max with the oxygen consumption (3.5 ml/kg/min) at rest. These assessments were again repeated on Day 90 of the ischemia reversal program and a percent change from the baseline reading was calculated.

Apart from these evaluations, the dependency of patients on standard allopathic medications on Day 1 and Day 90 of the ischemia reversal program was also assessed by computing and comparing the percentage of the total selected patients, who used a conventional allopathic therapeutic agent before and after the 90-day study period.

VO2 max and Metabolic Equivalents of Task (METs): The maximum volume of oxygen that an individual can consume during intense, wholebody exercise is called as VO 2 max. During exercise, the oxygen consumption in an individual increase as the exercise intensity increases until a point is reached when this consumption plateaus although the exercise intensity can continue to increase. This is defined as the VO 2 max or the maximum aerobic capacity of an individual.

In addition to VO 2 max, the energy cost of physical activities can also be expressed as METs. A MET is defined as the amount of oxygen consumed by an individual at rest (also known as resting energy expenditure) ie, approximately 3.5 ml/kg/min. Thus, a task at 2 METs would require two times the resting energy expenditure or 7.0 ml/kg/min. The METs are helpful in identifying the intensity of an individual's exercise routine.

For this study, the METs were calculated by dividing the oxygen uptake indicated by VO2 max by the oxygen consumption (3.5 ml/kg/min) at rest. The obtained METs were subsequently used to compute the DTS and were used to classify patients into three levels of exercise intensity: light exercise (<3.0 METs) an activity that results in only minimal perspiration and a very slight increase in breathing above normal; moderate exercise (3.0 to 6.0 METs) an activity that results in definite perspiration and above normal breathing; and heavy exercise (>6.0 METs) an activity that results in heavy perspiration and heavy breathing.

Duke Treadmill Score (DTS): Exercise stress test evaluations, using the exercise treadmill, are helpful in diagnosing the presence of significant coronary disease in patients with IHD symptoms and assessing their future risk towards undesirable cardiac events.[10]

Evaluations using exercise stress test offer the advantages of being non-invasive and cost-effective. Computing a prognostic DTS is a well-accepted and routinely used method that provides survival estimates based on the duration of an exercise test using a standard Bruce protocol, maximum deviation of the ST-segment (depression or elevation), and the presence and severity of angina during exercise. For the calculation of the DTS, the exercise time in the Bruce protocol can be replaced with METs.[11] In this study, we have used METs in place of the maximum exercise time in minutes to calculate the DTS using the below formula:

Duke treadmill score = METs – (5×ST segment deviation in mm) – (4×angina index);

where 0=no angina, 1=non-limiting angina, 2=exercise limiting angina.

The DTS is typically used for stratifying patients based on their risks and typically ranges from -25 to +15. A score of =+5 corresponds to a low-risk towards cardiac events and such patients do not appear to demonstrate a need for coronary angiography as a follow-up evaluation and generally exhibit a 4-year survival rate of almost 100%. An intermediate score ranging from -11 to +5 indicates moderate-risk towards cardiac complications and such patients are advised a coronary angiography based on their clinical status. On the other extreme, a score of =-11 classifies patients into the high-risk category with such patients requiring a coronary angiography for further evaluation and exhibiting a 4-year survival rate of around 79%. Additionally, the time for which a patient could exercise during the Duke treadmill test, until the observation of a 1 mm deviation (depression or elevation) of the ST-segment from the isoelectric line, was also recorded as the time to onset of ischemia.

Statistical Analysis:

The available data were pooled together and coded in a

Microsoft Excel spreadsheet using Excel 2019. Categorical data were presented in the frequency form whereas the continuous data were presented as mean (±SD). The McNemar-Bowker test was used to assess the METs and DTS before and after 90 days of treatment. The paired t-test was used to assess the difference between baseline values and values after 90 days of treatment. Box plot and histogram were used to represent the graphs, as appropriate.

RESULTS:

A comparison of the shifts in a patient's potential to perform strenuous activity was assessed using the METs utilization at baseline and after 90 days of therapy and is presented in Table 1.

Table 1: Shifts in the Metabolic Equivalents over time.

	Metabolic equivalent of task (MET)	After 90 days				p-value
		Light Exercise (<3.0 METs)	Moderate Exercise (3.0 to 6.0 METs)	Vigorous Exercise (>6.0 METs)	Total	
At Baseline	Light Exercise (<3.0 METs)	4	26	15	45 (21.63%)	<0.0001
	Moderate Exercise (3.0 to 6.0 METs)	1	26	76	103 (49.51%)	
	Vigorous Exercise (>6.0 METs)	0	1	59	60 (28.84%)	
	Total	5 (2.40 %)	53 (25.48%)	150 (72.11%)	N=208	

Overall, at baseline, 60 (28.84%), 103 (49.51%), and 45 (21.63%) patients were classified to the vigorous exercise, moderate exercise, and light exercise categories according to the utilization of their METs. Following 90 days of treatment in the ischemia reversal program, 150 (72.11%), 53 (25.48%), and 5 (2.40%) patients got classified to the vigorous exercise, moderate exercise, and light exercise categories according to the utilization of their METs. The average VO2 max improved from 16.72 ml/kg/min to 25.99 ml/kg/min (p-value <0.0001) resulting in a general improvement in patient METs that corresponded to a higher number of patients being able to undertake vigorous exercise. Subsequently, the time to onset of ischemia also exhibited a significant delay from 460.89 seconds observed at baseline to 700.17 seconds (p-value<0.0001) observed 90 days after starting the ischemia reversal program identifying the benefits of this program.

Similarly, a comparison of the shifts in patient risk potential, using the DTS at baseline and after 90 days of therapy, is presented in Table 2.

Table 2: Shifts in the Duke Treadmill Score over time

	Duke Treadmill Score	After 90 days				p-value
		Low risk (≥+5)	Moderate risk (-11 to +5)	High risk (≤-11)	Total	
At Baseline	Low risk (≥+5)	53	5	0	58 (27.88%)	<0.0001
	Moderate risk (-11 to +5)	50	53	0	103 (49.51%)	
	High risk (≤-11)	8	31	8	47 (22.59%)	
	Total	111 (53.36%)	89 (42.78%)	8 (3.84%)	N=208	

Overall, at baseline, 47 (22.59%), 103 (49.51%), and 58 (27.88%) patients were classified to the high-risk, moderate-risk, and low-risk categories according to their DTS. Following 90 days of treatment in the ischemia reversal program, 8 (3.84%), 89 (42.78%), and 111 (53.36%) patients got classified to the high-risk, moderate-risk, and low-risk categories per their DTS. The average DTS improved from -3.15 observed at baseline to +3.50 observed after 90 days of the ischemia reversal program (Figure 1). Thus overall, an improvement in the DTS that resulted in a shift from the higher risk categories to the lower risk categories was observed.

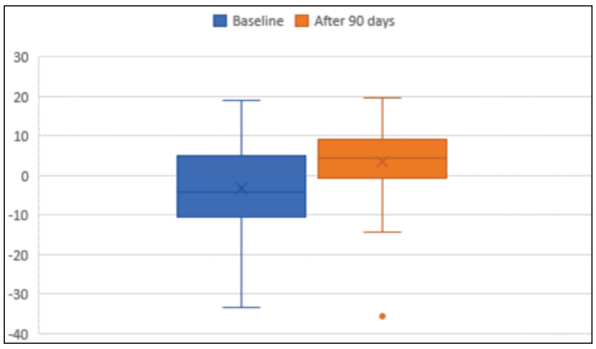

Figure 1: Comparison of Duke Treadmill Score.

The overall secondary clinical endpoints (body weight, BMI, SBP, and DBP) also showed significant improvement between the baseline values and 90 days after starting the ischemia reversal program (Table 3). The mean systolic blood pressure also attained near normal levels 90 days after starting the ischemia reversal program (p-value<0.0001). However, the mean diastolic blood pressure that was normal at baseline (78.41 mmHg) showed a significant decline to 75.12 mmHg although it was within the normal range (p-value<0.0001). The average body weight also exhibited a decrease from 68.26 kg to 64.62 kg (p-value<0.0001).

Table 3: Summary of mean change observed from baseline after 90 days for different parameters.

Parameter	Baseline	After 90 days	p-value
Weight	68.26±11.65 kg	64.62±11.06 kg	<0.0001
Body Mass Index	26.58±4.19 kg/m^2	26.07±13.76 kg/m^2	<0.0001
Systolic Blood Pressure	128.62±18.36 mmHg	122.35±15.59 mmHg	<0.0001
Diastolic Blood Pressure	78.41±10.09 mmHg	75.12±8.68 mmHg	<0.0001
Vo_2max	16.72±7.84 mL/kg/min	25.99±7.90 mL/kg/min	<0.0001
Time to onset of ischemia	460.89±229.66 seconds	700.17±179.68 seconds	<0.0001

The consumption of allopathic medications at baseline on Day 1 and 90 days after starting the ischemia reversal program are presented in Table 4 and Figure 2. Of the total subjects, 177 patients were on prescribed medications. The dependence of patients on most commonly prescribed medications (in =20% of the patient population) showed a decrease following 90 days of treatment in the ischemia reversal program and included antiplatelets (from 41.82% to 28.36%), beta blockers (from 39.90% to 26.92%), statins (from 35.57% to 17.78%), nonsteroidal anti-inflammatory drugs (from 34.61% to 24.03%), angiotensin II receptor blockers (from 31.73% to 22.59%), biguanides (from 28.84% to 15.38%), calcium channel blockers (from 24.51%to 18.26%), and nitrates (from 21.63% to 14.90%). Additionally, the percent of patients on no medications increased from 14.90% at baseline to 28.84% at 90 days after starting the ischemia reversal program.

Table 4: Consumption of Allopathic medication at baseline and post 90 days.

Medication	Baseline	After 90 days
Angiotensin II receptor blockers	66 (31.73%)	47 (22.59%)
B-blocker	83 (39.90%)	56 (26.92%)
Diuretics	22 (10.57%)	16 (7.69%)
Ca^{2+} channel blockers	51 (24.51%)	38 (18.26%)
NSAIDs	72 (34.61%)	50 (24.03%)
Biguanides	60 (28.84%)	32 (15.38%)
DPP4	13 (6.25%)	5 (2.40%)
Sulfonylureas	37 (17.78%)	25 (12.01%)
Antiplatelets	87 (41.82%)	59 (28.36%)
Statins	74 (35.57%)	37 (17.78%)
Nitrates	45 (21.63%)	31 (14.90%)
No medication	31 (14.90%)	60 (28.84%)

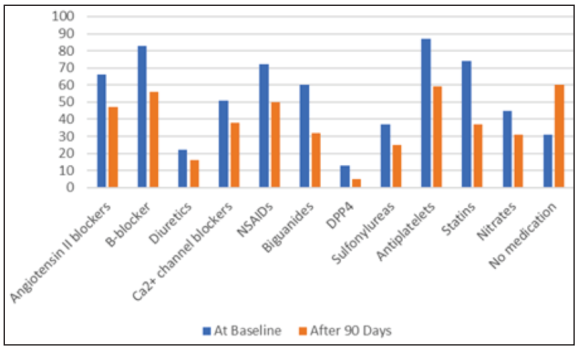

Figure 2: Reduction in Consumption of Allopathic Medication

DISCUSSION:

Despite several advances in medical science leading to a better understanding of IHD, availability of techniques to diagnose the condition, and the development of numerous drugs to control it, IHD continues to be one of the worldwide leading causes of mortality. One of the ways to reduce untimely deaths and improve the overall quality of life in patients with IHD includes providing cost effective alternatives that can be easily yet effectively administered and eventually lead to perceivable benefits to the patient. Regular administration of anti-ischemic drugs has provided therapeutic benefits in this chronic condition by exerting actions such as correction of imbalance between oxygen demand and supply to the heart, reduction of blood pressure, reduction of platelet aggregation, hypolipidemic action, and application of antioxidant effects to name a few. Several natural herbs regularly used in the practice of Ayurveda and alternative techniques also provide viable alternatives towards this aim.

The clinicians have developed an ischemia reversal program that is a combination of Panchakarma and allied therapies. The biggest advantage offered by the Panchakarma technique applied in the ischemia reversal program is that it can be administered as an add on procedure and coupled along with any other ongoing treatment regimens. Application of Panchakarma that forms the basis of the ischemia reversal program possibly provides its advantages through Snehana that reduces sympathetic overactivity by exerting anxiolytic effects leading to a reduction in blood pressure, Swedana that reduces myocardial oxygen demand via the reduction of sodium and water load, and Basti that helps in the release of nitric oxide from vascular endothelium using a decoction containing *Tribulus terrestris*, *Curcuma longa*, and *Emblica officinalis*. The nitric oxide released by the 3 herbs used in Basti acts through coronary vasodilation, antiinflammatory action, and antioxidant action[12-16].

The analysis of retrospective data obtained following the administration of the ischemia reversal program for 90 days exhibited significant improvements in the primary endpoints such as VO 2 max that was also used to compute the METs and DTS. A general improvement in the VO 2 max with the resultant METs corresponded to a higher number of patients being able to undertake vigorous exercise. The DTS also exhibited a shift from the higher risk categories to the lower risk categories. These improvements seen within the primary parameters led to a significant delay in the time to onset of ischemia. Additionally, significant improvements in the secondary endpoints such as BMI, SBP, and weight were also observed. Systolic blood pressure is one of the prognostic marker in patients with IHD as a reduction in this parameter leads to a reduction in the afterload of the ventricles and improves endothelial health. The study also demonstrated that ischemia reversal program noticeably reduced a patient's dependency on standard allopathic medication at the end of 90 days of therapy.[17,18]

Thus, the findings of this study identify that an improvement in the primary endpoints such as VO 2 max with the resultant METs and DTS can lead to an improvement in the time to onset of ischemia that in turn can result in a reduction in cardiovascular morbidity and mortality. The conduct of other such studies on a national scale, probably with larger sample size, two treatment arms to facilitate direct comparison with the standard therapy, and more follow up period can provide additional support to generalize the findings of this study for a larger population.

CONCLUSION:

As significant improvements in the primary endpoints (VO2 max with the resultant METs and DTS) and secondary endpoints (BMI, SBP, and body weight) were observed, the application of the ischemia reversal program can delay the onset of ischemia and help improve the overall quality of life in patients with chronic IHD.

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