Vidangadi Lauha' for Obese Type 2 Diabetes mellitus; Randomised controlled clinical study

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Article

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Abstract

Background Type 2 diabetes mellitus in obese persons is becoming alarming due to the increasing prevalence of its microvascular and macro vascular complications. Multitargeted treatment can be considered better than single targeted treatment in view of multiple pathways involved in the pathogenesis of diabetes and its complications.

Methodology-This open-label randomised controlled clinical study aimed to evaluate the clinical efficacy of '*Vidangadi Lauha*' (an *Ayurveda* formulation) in comparison with metformin for obese type II diabetes mellitus. Participants were divided into two groups. The trial group received *Vidangadi Lauha* 5 gm BID, and the control group received tablet metformin 500 mg BID for a duration of 3 months.

Results- Among 550 screened participants, 120 participants were eligible; out of them, 100 participants were enrolled and randomised by a computer-generated method, **and** of them, 80 patients (40 in each group) completed the trial. *Vidangadi Lauha* showed a reduction in HbA1c from 8.048 (0.95) to 7.14 (0.73), while metformin showed a reduction in HbA1C from 8.3 (0.99) to 7.18 (0.67).

Conclusion-Both treatments were equally effective in reducing blood sugar fasting (F), postmeal (PM) glycated haemoglobin (HbA1C) and body mass index (BMI).

Vidangadi Lauha is more effective in reducing *Ayurvedic* symptoms, waist hip ratio and cholesterol than metformin. High-density lipoproteins (HDLs) were improved by minor clinical differences in both groups. Neither treatment had a statistically significant effect on reducing low-density lipoproteins (LDL).

Introduction

Obese type 2 diabetes mellitus is a multifactorial, noncommunicable disease caused by disturbances in the metabolism of carbohydrates, fat, and protein and due to disturbed insulin secretion or its action or both. It is the most life-threatening disease due to its increasing prevalence of microvascular and macro vascular complications.

A report from the Indian Diabetes Federation shows that nearly 463 million people are living with diabetes, which will increase to 578 million by 2030. It will continue to increase 700 million by 2045. This number will jump up to 700 million by 2045. The ratio of diabetic individuals to healthy individuals was 1:11 in the 20-79 age group. Nearly 10% of global expenditure is spent on diabetes. Three out of 4 people with diabetes live in low- and middle-income countries. ^[1]

The therapeutic approach for managing type 2 diabetes should not be limited to glycemic control but should also prevent complications due to diabetes. Currently, *Ayurveda* formulations are more

popularly used as oral hypoglycemic agents with the belief that they do not have any side effects and minimize the risk of complications due to diabetes mellitus. Various classical Ayurveda formulations have many phytochemicals that act symbiotically and exhibit pharmacodynamic actions^[2]. Multitargeted Ayurveda formulations can be considered important to bring about breakthroughs in the treatment of type 2 diabetes if supported by scientifically designed clinical trials. It is also expected that the bedside-to-bench approach is more suitable for various studies on Ayurveda formulations. (3)

Methodology

This study was a randomised open-label controlled clinical trial conducted as per the CONSORT statement for adherence to clinical trials. The study was conducted after approval from the Institutional Ethics Committee, Government Ayurveda College, Nagpur, India (approval number PGS/465/2018) and prospective registration in the Clinical Trials Registry government of India (CTRI/2019/02/017609). Participants were recruited for the study through OPD, casualty, and various camps following written informed consent. Fig 1 describes the flow chart of the clinical trial.

Formulation- Vidangadi Lauha

'*Vidangadi Lauha*' is a classical Ayurveda formulation mentioned in '*Bhaishajya Ratnawali*' (a classical *Ayurveda* text) and was prepared as per classical Ayurveda methods.^[183]

After identification of raw material for formulation, i.e., fruit of *Embelia ribes* (Batch No-VF01), rhizome of *Piper nigrum* (Batch No-S01), *Cuminum cyminum* (Batch No-SJ01), fruit of *Piper longum* (Batch No-PF01), rhizome of *Cyperus rotundus* (Batch No-MR01), fruit of *Emblica officinalis* (Batch No-AF01), fruit of *Terminalia chebula* (Batch No- HF01), fruit of *Terminalia bellerica* (Batch No-BF01), and *Lauha Bhasma* (Batch No-LB01) were sent for standardisation.

After raw material standardisation, *Vidangadi Lauha* (Batch No-VL01) was prepared as per the classical method. The prepared formulation was again standardised for finished product standardisation. We ensured that the qualities of all the raw material and final products matched the *Ayurvedic Pharmacopodia of India* (API) guidelines for the standardisation of *Ayurvedic* medicine. Preparation of the formulation and its standardisation were performed by Unijules Pharma Nagpur, India.

Trial Participants

Initially, persons willing to screen for diabetes were screened on the basis of the Indian Diabetes Risk Score (IDRS). If IDRS > 50, then they were advised for BSL fasting and BSL postmeal, after which they were enrolled/excluded as per the inclusion and exclusion criteria.

Inclusion and exclusion criteria

People aged between 30 and 70 years, newly diagnosed obese type 2 diabetes mellitus (BMI 23-30), fasting blood sugar level 126 mg/dl to 200 mg/dl and postprandial blood sugar level 200

mg/dl to 300 mg/dl, HbA1c from 6.5% to 9%, fulfilled criteria of diagnosis and had signs and symptoms of *Sthula Madhumeha* as per Ayurveda clinical evaluation, patients with controlled hypertension BP<150/90 mm of hg and those who were willing to give informed written consent included in the study were included in the study.

The exclusion criteria were people currently taking oral hypoglycemic agents who were diagnosed with diabetes mellitus (fasting blood sugar level >200 mg/dl and postmeal blood sugar level>300 mg/dl, HbA1c less than 6.5% and more than 9%, BMI less than 23 and above 30.) Patients with insulin-dependent diabetes mellitus and juvenile diabetes; complications such as vasculopathy, nephropathy, retinopathy and neuropathy; other systemic complications such as hepatic, renal and cardiac problems; any complications arising during treatment or if any patient discontinued the treatment; poorly controlled blood pressure; lactating females; emergency cases in Type 2 Diabetes Mellitus; and patients who were currently participating in any other clinical trials (since last 6 months) were excluded from the study. Those who were not willing to participate in the trial and who were not ready to give written consent were also excluded.

Sample size

Sample size 80 (40 in each group) was calculated considering the hypothesis of an equivalence trial. We hypothesised that both *Vidangadi Lauha* and metformin would be equally effective in reducing HbA1c at the end of 3 months with a 95% confidence interval and at least 80% power of the study using open Epi freely available software.

Trial Protocol

Initially, general and systemic examinations of the participants were performed. Clinical symptoms of obese type 2 diabetes mellitus were assessed and recorded in a case record form (CRF). Baseline investigations that included complete blood count with erythrocyte sedimentation rate, blood sugar level fasting and post meal, glycated haemoglobin, urine routine and microscopic, lipid profile were performed.

Participants were randomised by a computerised random number generator to either the trial group (*Vidangadi Lauha*) or the control group (metformin). Those in the trial group were given 5 gm *Vidangadi Lauha* twice daily, taken orally (before meals) with 100 ml lukewarm water for 90 days.

Those in the control group were given metformin 500 mg twice daily (with meals) for 90 days. All the participants were advised to continue a routine diet but stopped direct sugar intake. A 1-month stock of medicine was provided to participants at each visit.

Participants were called to the Government Ayurved College and Hospital Nagpur every month (on the 30th, 60th, and 90th days) for follow-up after the baseline visit. Fasting and postmeal blood sugar levels were determined at each follow-up. General and systemic examinations, clinical assessments, BMI, abdominal circumference, and waist-hip ratio were also performed at each

follow-up. Complete blood count, ESR, HbA1c, routine urine tests and microscopy were performed at baseline and after 90 days. All these observations of each participant were recorded in a case record form at every follow-up. The participants were monitored for clinical improvement in clinical, physical, and pathological parameters and for adverse drug effects.

To assess the effect of medicines on Ayurvedic clinical symptoms, the index was used as per Nakanekar et al.(4)

Statistical analysis

To describe the sociodemographic data of this study, numbers and proportions were used. Continuous data from this study were described by using means and standard deviations. The chi square test was used to analyse the difference between the two groups at the end of the study. A p value of 0.05 or below was considered statistically significant. Statistical analysis was performed using GraphPad Instat 5. Statistical analysis is mentioned in Tables 1 and 2.

Results

Study population

Five hundred fifty participants were screened to assess eligibility. Of the forty-six patients who withdrew their consent, two hundred ninety met the exclusion criteria and were excluded. Among these 120 participants who were eligible, 100 participants were selected for the randomised computer-generated method. The participant distribution is shown in the CONSORT flowchart (fig 1).

Baseline characteristics

The overall median age of the participants in the trial group was 54 years (interquartile range [IQR] – 35-70) and that of the participants in the control group was 59 (IQR 32-70). Twenty-six percent were females in the trial group, and 20% were females in the control group. In the trial group, 5% of patients had a positive family history of diabetes, while 11% of patients in the control group had a family history.

The majority of participants in the trial group had *Kapha-Pitta Prakriti* (13%), while the majority of participants in the control group had *Vat-Pitta Prakriti* (11%). The majority of participants in the trial and control groups had *Vishamagni* (17% and 21%, respectively).

Effect Analysis

Mean fasting and postmeal blood sugar levels in both groups decreased significantly over the course of 3 months of treatment. There was a significant reduction in glycated haemoglobin in both groups. The trial group drug was more effective in reducing the waist-hip ratio than the control group drug. Both groups were equally effective in reducing body mass index.

There was a significant reduction in the Ayurveda clinical score in the trial group compared to the control group, which suggests more symptomatic relief in trial group participants. The maximum number of patients in the trial group was moderately cured, i.e., Forty-five percent of patients in the trial group were moderately cured. In the control group, 55% of patients were mildly cured. In the control group, 40% of patients were moderately cured. Five percent of patients in the trial group were markedly cured. A total of 7.5% of patients in the trial group and 5% of patients in the control group were unchanged after completing the treatment of the respective groups. This means that both treatments are equally effective while looking for overall efficacy.

Discussion

Obese type 2 DM is now epidemic worldwide. The gut microbiome has a bidirectional association with obese type 2 DM. [5] In obese individuals, there is a decrease in the gut microbiota. The human gut microbiota enables the extraction of energy components. In obese diabetes, there is low-grade inflammation. Published data indicate that gut modulation decreases inflammation in various ways; for example, metabolites from gut microbiomes responsible for modulation of gut microbiota also contribute to gut barrier function. [6]

In Ayurveda, obesity type II diabetes mellitus can be correlated with *Sthul Madhumeha*. Ayurveda assumes pathogenesis and treatment of obese type 2 diabetes mellitus, through gut-centric approach. There are two main vitiation factors: *Agni* and *Rasa Dhatu*. *Agni* (metabolic power) is a physiological phenomenon in the body that is responsible for digestion, absorption and bio assimilation of all micronutrients. As per Ayurveda classics, *Aama* (toxic material) is produced when there is disturbance in *Agni* (digestion). *Rasa Dhatu* is the first primary base for the formation of all tissues in the body during digestion. According to Ayurveda, all cascades of the pathogenesis of diabetes start in the gut, and disturbances in the formation of diabetes occur in the gut. [7]

Diabetes is a metabolic disorder involving the disturbance of carbohydrate, fat, protein metabolism and insulin secretion and its action. The gut microbiota also plays an important role in type II diabetes mellitus (DM) and obesity. [8] Glucagon-like peptide 1 stimulates insulin secretion by acting on incretin hormones and is responsible for the inhibition of glucagon secretion and decreases gut motility. [9]

If metformin is given for a longer duration, there are side effects. Some research papers provide evidence that metformin affects the status of vitamins B₁, B₁₂, D, folic acid and magnesium as well as causes disruption to the microbiome, all of which may to some extent predict the desired outcomes with this medication. Given that the status of these micronutrients in patients with T2DM is already likely to be suboptimal and that these deficiencies are variously associated with diabetic complications such as compromised endothelial, microvascular, vascular and neurological function [10],

Some herbs used in the formulation *Vidangadi Lauha* formulation have alpha glucosidase inhibitory activity^[11], antidiabetic^[12,13], anti-dyslipidaemia^[13,14], hypoglycaemic^[15], and beta cell protective activity^[16]. Prevention of platelet aggregation and thrombus formation^[17] inhibited the activities of α amylase, α -glucosidase, dipeptidyl peptidase-4^[18], anti-obesity^[19], endothelial dysfunction, oxidative stress, and systemic inflammation^[20]. Thus, '*Vidangadi Lauha*' can be a very good formulation for the prevention of multiple complications of type 2 diabetes.

Limitations of the Study

Liver function tests and kidney function tests of all the patients were not performed. Inflammatory biomarkers in obesity, such as adiponectin, leptin, ghrelin, ferritin, and C-reactive protein, were not measured before and after treatment due to economic constraints. In this study, blood sugar levels were measured at 0, 30, 60, and 90 days of treatment, as the blood sugar level is a variable parameter that should be done frequently or the CGM system should be used for blood sugar monitoring.

Future Scope

This study was conducted in an Indian population. There is a need to conduct studies in different populations to determine genetic variation or the effect on genetics.

As in developing countries, the maximum number of type 2 diabetes cases is in the 40- to 60-year-old working group. The cost-effective, safest Ayurveda medicine is beneficial to this age group. According to Ayurveda, the treatment varies according to *Prakriti* and the status of *Dosha*, *Dushya*, and *Mala* in patients. There is future scope to conduct this study in different kinds of *praakriti* of patients and see the genetic correlation between this.

As type 2 diabetes mellitus is a chronic disease, it is evident that most diabetic patients are diagnosed when complications develop. Complications in type 2 diabetes mellitus develop after 5 years. There is a need to research which stage of diabetes *Vidangadi lauha* is more beneficial.

Conclusion

Vidangadi Lauha can be a new indigenous candidate with multitargeted action for the treatment of newly detected obese type 2 diabetes.

Declarations

Conflict of Interest- Nil.

Informed Consent- All the patients involved in the study have given written informed consent.

Source of Funding- We have not received any funding for this study.

Author Credits-

Data Collection- PK,

Supervision and Monitoring- JG

Drafting protocol, drafting manuscript, Critical Edits, Statistical analysis- AN

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Tables

Table 1 Effect of Therapy before and after treatment

	Trial Group (Vidangadi Lauha n=40)		Control Group (Metformin ,n=40)	
Variables	BT	AT	BT	AT
Mean HbA1c (SD)	8.048(0.9542)	7.14(0.73)	8.3(0.9923)	7.18(0.67)
Mean Total leucocyte count	6967(1755)	7031 (1340)	7682(1600)	7624(1245)
Mean hemoglobin	11.84(1.292)	11.95(1.19)	11.87(1.558)	12.20(1.376)
Mean ESR	17.85(13.35)	11.55(4.846)	15.57(5.52)	12.85(5.077)
Mean Total cholesterol	192.32(43.39)	160.07(44.81)	165.84(34.72)	150.87 (27.94)
Mean HDL	43.03(9.15)	45.41 (10.73)	43.75(11.06)	46.52 (11.40)
Mean LDL	105.30(31.61)	99.73 (38.93)	107.79(32.92)	104.53 (24.72)
Mean VLDL	35.89(18.57)	31.47 (16.69)	30.94(14.33)	26.33 (12.11)
Mean Triglycerides	183.42(78.72)	145.72 (52.80)	153.11(60.46)	143.24 (47.91)
Mean Abdominal circumference	94.3(7.940)	91.96(7.778)	93.525(6.571)	92.39(6.178)
	BT(n=12)	AT(n=12)		
SGOT	37.85±12.89	36.62±7.92	Not Done	Not Done
SGPT	30.76±15.37	34.37±11.55	Not Done	Not Done
Billirubin Total	0.65±0.23	0.64±0.16	Not Done	Not Done
Billirubin direct	0.227±0.25	0.1454±0.076	Not Done	Not Done
Blood Urea	20.78±7.82	14.16±2.8	Not Done	Not Done
Creatinine(N=13)	0.98±0.28	0.87±0.21	Not Done	Not Done
Uric Acid	4.97±1.33	0.46±0.92	Not Done	Not Done

Table 2 Effect of Therapy on Folllow up parameters

	Follow up period	Baseline	30 th day	60 th day	90 th day
Trial group	Fasting	151.65±26.25	139.32±25.16	132.45±19.760	117.2±19.428
	Post meal	248.3±28.699	227.05±27.397	189.77±20.59	162.92±42.85
	BMI	26.195±2.563	25.866±2.556	25.153±2.464	24.45±2.495
	Ayurveda Symptom score	29.12±6.68	22.3±4.445	14.7±2.857	6.625±2.924
	Waist hip ratio	0.9325±0.075	0.9195±0.074	0.865±0.1536	0.8687±0.052
Control Group	Fasting	157.5±27.51	146.9±25.048	135.62±20.162	114.9±19.248
	Post meal	247.52±32.67	224.5±25.30	182.1±26.897	161±22.628
	BMI	25.96±2.196	25.78±2.160	25.44±2.177	25.133±2.316
	Ayurvedic score	33.05±7.528	28.325±6.285	21.125±4.513	17.875±4.845
	Waist hip ratio	0.88±0.058	0.8795±0.057	0.838±0.2008	0.874±0.053

Figures

Figure 1

CONSORT Flow Diagram