Double Blind Placebo Controlled Clinical Trial of an Antidiabetic Ayurvedic formulation, *Amree Plus* for its efficacy & toxicity in Type 2 Diabetes Mellitus patients

FINAL REPORT
(NI - 536)

SUBMITTED BY:

DR.ANOOP MISRA
PROFESSOR
DEPARTMENT OF MEDICINE
ALL INDIA INSTITUTE OF MEDICAL SCIENCES
NEW DELHI-110029

SRB CENTRE OF CLINICAL PHARMACOLOGY
ALL INDIA INSTITUTE OF MEDICAL SCIENCES
NEW DELHI-110029

Principle investigator

Dr. Anoop Misra
Professor
Department of Medicine
All India Institute of Medical Sciences, New Delhi.

Dr. Anoop Misra
M.D.,M.A.M.S., FIMSA
Professor of Internal Medicine
All India Institute of Medical Sciences
Ansari Nagar, New Delhi-110 029

Co- investigators

Mrs. Rekha Sharma
Chief Dietician
Department of Dietetics
All India Institute of Medical Sciences, New Delhi

Dr. R M Pandey
Professor & Head
Department of Biostatistics
All India Institute of Medical Sciences, New Delhi.

Dr. Randeep Guleria
Professor
Department of Medicine
All India Institute of Medical Sciences, New Delhi.

Research Team

Research Officers

Dr.Vidya Kumari
Dr.Deepti Jain

Dieticians

Mrs. Kavita Rastogi
Ms.Vasundhara Singh

Place of the study
Department of Medicine
All India Institute of Medical Sciences New Delhi-110029

Duration of the study
4th September 2001 to 31st July 2004

Funding Agency
Aimil Pharmaceutical (I) Ltd. New Delhi

INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Overt diabetes affects 2-3% of the total world population. Although diabetes has been a known morbidity since times immemorial, its incidence has been growing notably in the present times and is projected to reach the dimensions of an epidemic.

Over the years a number of new facts have emerged regarding the pathology and the therapeutic factors of diabetes. Scientists have succeeded in throwing adequate light on the etiopathogenesis of diabetes including its genetic diathesis. Diabetes mellitus continues to be a major threat to the millions of masses due to acute diabetic episodes or its complications. It is pertinent to mention that the hallmark of the problem of diabetes in the present times is the wide range of complications which a diabetic patient insidiously develops leading to respective organ failure and death. The main issue in the management of diabetes swings between the prevention and the management of the complication of diabetes rather than the treatment of diabetes itself.

Vidya Kumari

It has become possible to achieve significant metabolic corrections in diabetic patients with the use of a variety of anti-diabetic drugs, but the fact remains that these synthetic molecules pose several side / adverse effects, which may sometimes be life threatening, thus limiting their use.

The alternative system of medicine is being looked into for newer drugs which can provide effective control of hyperglycaemia and prevent / delay the onset of complications associated with Diabetes Mellitus.

AIMS & OBJECTIVES

The clinical evaluation was carried out to investigate the alternative system of medicine with a view to research and scientifically validate the herbal preparations.

The acceptance of these herbs / herbal preparation has increased tremendously not only in our country but world over due to their practically safer approach, no side effects and improvement in the quality of life by helping maintain euglycaemic levels and preventing / delaying the onset of diabetic complications. Another reason for taking this product for clinical evaluation was the scientific validation of its ingredients / the formulation as a whole in a number of researches and clinical trials.

The Ayurvedic formulation, *Amree Plus* was chosen for the study since it is a quality medicine duly approved by the Drugs Control Department and was already in market.

To evaluate the effect and tolerance of Ayurvedic anti-diabetic formulation, Amree Plus Granules, on glycaemic control in mild to moderate Type 2 diabetes mellitus patients by conducting Double Blind Randomized Placebo controlled clinical trial.

Vidya Kumari

INGREDIENT HIGHLIGHTS OF AMREE PLUS GRANULES

Karela	*Momordica charantia*	Possess insulin like molecules and acts as pancreas toner by intensive metabolic regulation in diabetes
Vijaysaar	*Pterocarpus marsupium*	
Bimbi	*Coccinia indica*	
Jamunpatr	*Syzigium jambolana*	
Neem Patr	*Azadirachta indica*	
Paneer Dodi	*Withania coagulans*	
Sadabahar	*Catharanthus roseus*	
Methi Seeds	*Trigonella foenum graecum*	Delays absorption of glucose from GIT.
Haridra	*Curcuma longa*	Preventive role on the oxidative stress in Diabetes mellitus, lipid metabolic regulator & immunomodulator
Giloe	*Tinospora cordifolia*	
Amla	*Emblica officinalis*	
Ashwagandha	*Withania somnifera*	
Tulsi	*Ocimum sanctum*	
Punernava	*Boerhaavia diffusa*	Helps significantly in delaying damage to the kidneys
Shatavar	*Asparagus racemosus*	Provides essential nutrients
Sunflower Seeds	*Helianthus annus*	
Tejpatr	*Cinnamomum tamala*	Helps improve metabolism
Kumari	*Aloe vera*	
Ginger	*Zingiber officinalis*	

Vidya Kumari

METHODOLOGY

Hospital Ethical committee of All India Institute of Medical Sciences approved to conduct the project "Double blind placebo controlled randomized trial of the compound *Amree Plus* in mild to moderately severe cases of type 2 diabetes mellitus". The clinical trial of 16 weeks duration for each patient was initiated from 3rd October 2001.

Amree Plus, an anti diabetic product was selected for the clinical evaluation of its efficacy and safety in regulating Glycemic parameters viz., fasting and post-prandial blood glucose levels, glycosylated hemoglobin, insulin levels, and LFTs, KFTs & Lipid Profile.

700 Patients from medicine OPD and Diabetic clinic at AIIMS were screened, out of which 100 patients were selected after applying inclusion and exclusion criteria. For screening; haemogram, LFT, RFT, chest x-ray and urine routine tests were done. Fundus examination was done by ophthalmologist. Patient information sheet was provided to the patients.

Informed consent was obtained from the patients before the study.
At the baseline serum insulin - fasting and post prandial, blood glucose - fasting and post prandial, glycosylated hemoglobin, Lipid Profile tests were done.

The trial duration of 16 weeks was preceded by a placebo run-in period of 4 weeks. During placebo run-in period patients were advised to follow diet as per the diet chart given by the dietician and they were to follow exercise as advised. After run in period of 4 weeks patients were randomized into placebo and drug arms for 16 weeks. Their ongoing anti-diabetic treatment was continued and even augmented if needed (dosage of medicine could also be reduced in certain cases in drug arms) with the intention to treat the patients.

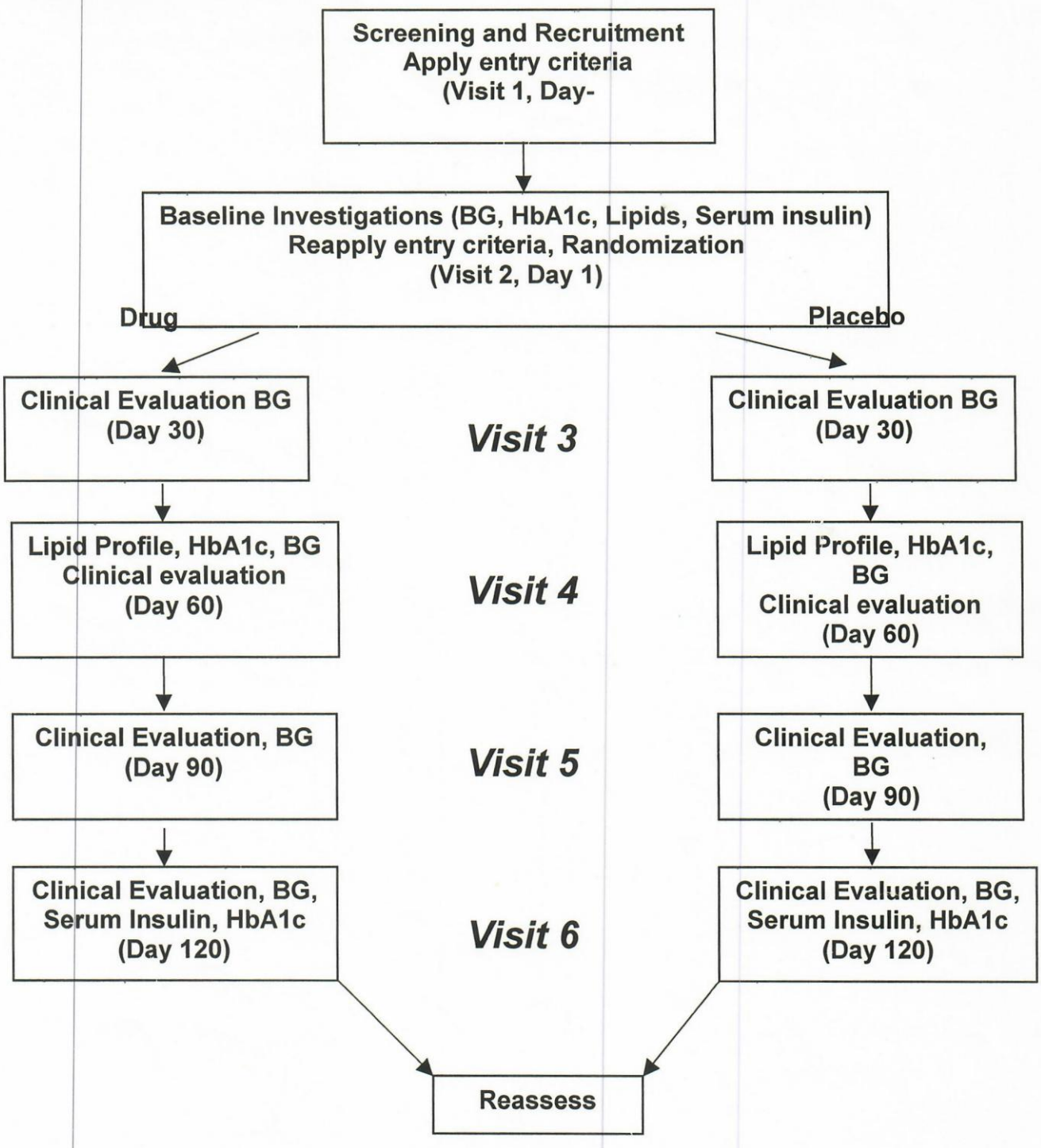
Vidya Kumari

Patients were given 5 gm pack of granules (black colored with characteristic flavor) containing either placebo or *Amree Plus* Granules and were advised to take one pack thrice a day before meals. Each box of granules pack was given a particular code number ranging from 1 to 100. These patients were reviewed every month for fasting and two hourly post parandial blood glucose and next lot of medicine was given to them. After two months (in between the study) glycosylated hemoglobin and lipid profile was repeated, and after four months on completion of the study(visit 6, day 120)) serum insulin - fasting and post prandial, blood glucose - fasting and post prandial, glycosylated hemoglobin, Lipid Profile, haemogram, glycosylated hemoglobin, lipid profile LFT, KFT and urine routine tests were repeated. Fundus examination was done by ophthalmologist.

The study was conducted with an intention to treat the patient and if at any time the treating physician felt that blood glucose control was inadequate, appropriate drug regimen was augmented accordingly. On completion of study, the codes of patients were decoded to find out whether the patient had received drug or placebo after randomization. Their bio-chemical parameters at study termination (visit 6, day 120) were compared with base line (visit 1, day 30) statistical analysis was performed by paired or unpaired t test for numerical variables and chi square test for ordinal.

Vidya Kumari

Assessment Method



Vidya kumari

The patients underwent a detailed clinical and bio-chemical evaluation before and during the study. Blood samples were analyzed for fasting blood sugar (FBS), post prandial blood glucose (PPBS), glycated hemoglobin (HbA_{1c}) immuno-reactive insulin (IRI), renal and hepatic indices & lipid profile.

Analytical Methods

Blood sugar, total cholesterol and triglycerides were estimated by Randoxx Kit, HDL and HbA1c by manual method, Serum Creatinine and Urea by Auto Analyzer (Hitachi 717) using enzymatic kinetic method, SGOT & SGPT BY IFCC (International Federation of Clinical Chemistry) using Hitachi 717 model, Hemogram was done by Coulter Maxon and ESR was estimated using Wintrobe's method. Routine and Microscopic examination of urine was also done. Insulin was measured using Insulin Immuno Assays.

Statistical Methods

Data was entered prospectively into excel sheets and after the entry data was analysed for variability using STATA, Version 8.0, 2003. Mean difference of blood glucose response from baseline between the two groups (*Amree Plus* and Placebo) was compared by two sample Wilcoxon ranksum (Mann-whitman) test.

INCLUSION CRITERIA

- Type 2 Diabetes mellitus, diagnosed on oral glucose tolerance test according to WHO criteria and on stable doses of oral hypoglycemic agents for last 3 months.
- Fasting blood glucose between 120-200 mg%
- 2 hours post-prandial blood glucose between 140-250 mg%.
- HbA1c < 9%

Vidya Kumari

EXCLUSION CRITERIA

- Patients unwilling to participate
- Pregnancy
- Severe end organ damage (congestive cardiac failure, renal failure etc.)
- HIV infection
- Any acute or chronic illness of severe nature

OBSERVATION & RESULTS

100 patients (55 males & 45 females) with Type II NIDDM were evaluated in the study There were 50 in the treatment group (drug arm) and 50 in placebo group (placebo arm)

Mean age of the patients in the Amree plus group was 46.18 $\pm$ 9.8 and mean age in the placebo group was 47.94 $\pm$ 10.4. Average weight in the Amree Plus group was 62.91 $\pm$ 10.9 and in placebo group it was 67.19 $\pm$ 10.8. BMI in Amree Plus group was 25.04 $\pm$ 3.7 and placebo group had an average BMI of 26.17 $\pm$ 4.3.

Biochemical results of all the patients who completed the study were analyzed. 1 patient was withdrawn from study as she developed mild reaction (urticarial rashes & gastroenteritis) during visit 5 (day 90) and 4 patients were lost to follow-up after visit 5 (day 90). Decoding revealed that the patient who developed hypersensitivity reaction and one patient who was lost to follow up were on drug & the other 3 patients who were lost to follow up were on placebo.

Statistical analysis revealed that effect on fasting blood glucose was more than post-prandial blood glucose. Table below shows mean blood sugar fasting, blood sugar post-prandial, glycosylated hemoglobin, renal function tests by creatinine levels and liver function tests by SGOT and SGPT.

Vidya kumari

Table showing the results on the total patients taken for the clinical trial by comparing Amree Plus & Placebo groups

	Variables	Amree Plus	Placebo	p value
At base line	FBS (mg.%)	152.76±22.2	144.18±18.9	0.04
	PPBS (mg.%)	201.48±34.9	196.76±31.4	0.47
	HbA1c	8.25±0.4	8.13±0.4	0.21
Post therapy	FBS (mg.%)	142.54±37.01	142±28.3	0.94
	PPBS (mg.%)	193.38±53.6	191.85±43.5	0.30
	HbA1c	8.05±1.01	8.26±0.9	0.35

Table showing the results on the patients who responded well to Amree Plus along with Placebo by comparing Amree Plus & Placebo groups

	Variables	Amree Plus
At base line	FBS (mg.%)	161.51±43.4
	PPBS (mg.%)	205.80±67.8
Post therapy	FBS (mg.%)	124.70±40.3
	PPBS (mg.%)	175.16±64.8

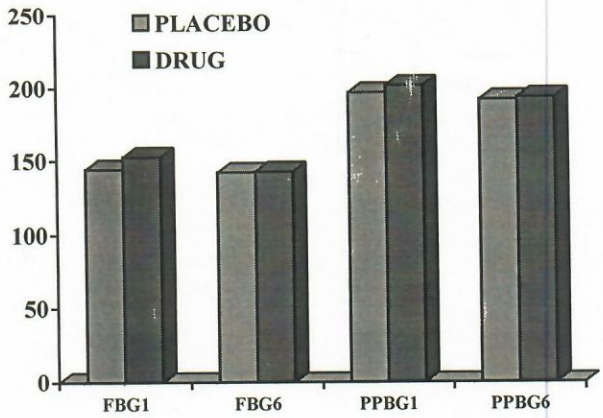
Highly significant results were observed in 27 (54%) patients in the drug arm. Blood sugar fasting showed reduction from 161.51 to 124.70 (22.8%) in the Amree Plus group whereas the placebo group had a decline of only 2-4%. A decrease from 205.80 to 175.16 (14.89%) in Post-prandial blood glucose was noticed in the patients on drug whereas the placebo group revealed a decline of only 3-4%.

Table showing the results on the total patients related to other biochemical parameters by comparing Amree Plus & Placebo groups

	Variables	Amree Plus	Placebo	p value
At base line	Creatinine mg.%)	1.00±0.1	0.91±0.1	0.00
	SGOT (units)	30.18±10.4	30.86±13.04	0.77
	SGPT (units)	32.28±15.4	35.48±20.2	0.37
Post therapy	Creatinine mg.%)	0.92±0.1	1.34±2.8	0.41
	SGOT (units)	27.22±6.3	33.91±35.5	0.30
	SGPT (units)	28.06±7.3	37.93±31.5	0.09

Vidya Kumari

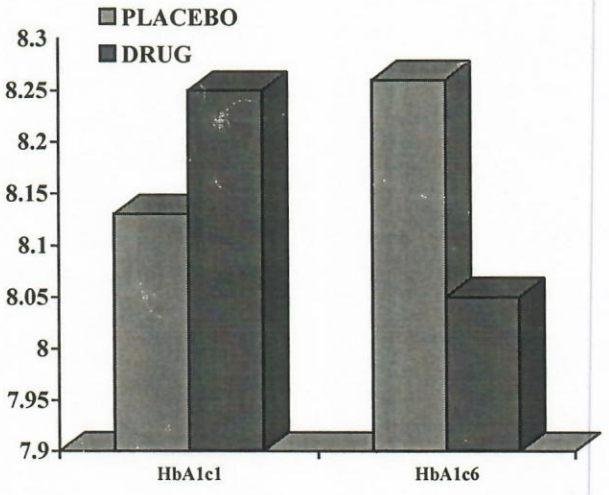
Comparison between means of blood glucose values in drug and placebo arms at visit 1 and 6



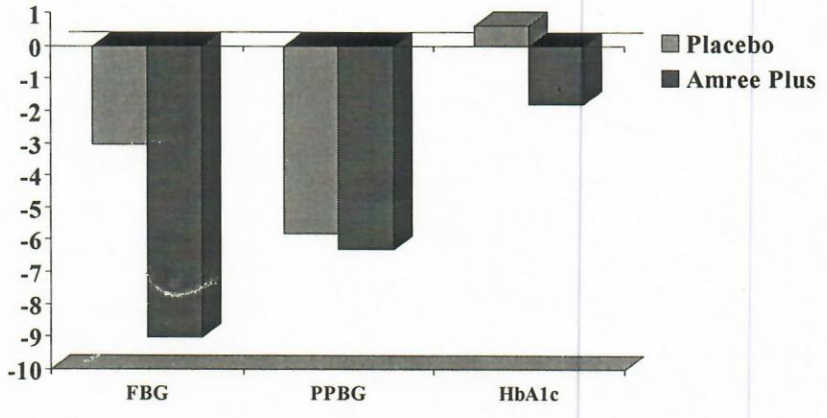
Vidya Kumari

Glycosylated Hemoglobin decreased from 8.25±0.4 to 8.05±1.01, which is around 15% decline from the elevated level, in patients receiving Amree Plus. On the other hand, there was an increase in HbA1c in the placebo group from 8.13±0.4 to 8.26±0.9 during 4 months trial period.

Comparison between means of glycosylated hemoglobin in drug and placebo arms at visit 1 and 6



Percentage changes in glycemic parameters at visit 6 in drug and placebo arms



Vidya Kumari

Another observation that was made during the study was, **Amree Plus group patients responded well with OHG's as compared to those on placebo. Lowering of blood glucose and maintenance of HbA1c was much more marked in patients receiving Gliclazide.** Favorable response in lipid profile was seen in all the patients on drug. Datas of insulin assay also reveal better utilization of insulin and in some cases remarkable modulation of insulin was observed.

DISCUSSION & CONCLUSION

Amree Plus showed promising anti-hyperglycaemic activity in patients with type 2 diabetes mellitus with respect to glycaemic parameters.

It is probable that Amree Plus helps regulate the metabolic activities by activating the liver for effective utilization of glucose and also supplements the much-needed essential micronutrients for the health of diabetic.

Appreciable improvement in liver and kidney function tests as denoted by lowering of SGOT, SGPT & S.Creatinine was observed. Hence, Amree Plus may prove to be of immense value in preventing / delaying the onset of diabetic complications.

There was significant improvement in the feeling of well-being due to better control of hyperglycaemia and availability of micronutrients from the herbal formulation Amree Plus.

It is further suggested that Amree Plus should be studied extensively as adjunctive therapy in patients with Type 2 Diabetes Mellitus.

Vidya Kumari