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Research Article

Comparison of conventional and sustained-release formulation of metformin in type 2 diabetics

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ABSTRACT

Background: To investigate the effects of metformin sustained-release (MSR) compared with metformin immediate-release (MIR) on glycaemic control, blood pressure, lipid profile and metabolic parameters like weight, waist circumference in type 2 diabetes.
Methods: A prospective, randomized, double blind study was conducted at tertiary healthcare and teaching hospital at Pune, Maharashtra. After obtaining institutional ethical committee approval and written informed consent, 40 newly diagnosed type 2 diabetic patient were randomly assigned to receive metformin immediate release formulation (MIR) 500 mg once 1 week and then twice daily and metformin sustained release formulation (MSR) 500 mg once 1 week and then 1000mg once daily for 18 weeks. Fasting and post prandial blood glucose level (BGL), HbA1c, blood pressure, lipid profile, weight and waist circumference, were recorded at the start and end of study.
Results: Both MIR and MSR significantly decreased fasting; post prandial BGL and HbA1c at 18 weeks. But no significant difference was seen between two groups. Study did not show any effect on blood pressure and on lipid profile. Both formulations decreased obesity as evident by significant reduction in weight and waist circumference. All patients tolerated both formulations of metformin. Though overall incidences of adverse effects are less with sustained release formulation, difference was not significant between two groups.
Conclusions: To conclude, both metformin immediate release and sustained release formulations achieved comparable glycaemic control and sustained release formulation would be as effective as immediate release formulation with advantage of being reduce daily intake of tablets.

Keywords: Metformin, Sustained release, Tolerability

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the health care system.[1]

Metformin, a biguanide oral antihyperglycaemic agent, is widely used in the treatment of type 2 diabetes. Metformin lowers hyperglycaemia in patients with type 2 diabetes through reducing glucose overproduction in the liver and enhancing glucose uptake in skeletal muscles, which are contributable to the improvement of insulin sensitivity[2] probably via the activation of adenosine monophosphate (AMP) - activated protein kinase.[3] In UK prospective diabetes study, it has been demonstrated that intensive glucose control with metformin appeared to decrease the risk of diabetes-related end-points including macro vascular complications in overweight diabetic patients and was associated with less weight gain and fewer hypoglycaemic events than that with insulin and sulphonylureas.[4] Because of its unique mechanism of action and cardiovascular advantage and proven safety profiles, metformin has been recommended by the International diabetes federation and the other professional groups as the initial option for pharmacotherapy in patients with type 2 diabetes.[5-6] The therapeutic profile of metformin has been established over three decades of clinical use, largely using an immediate-release formulation that requires

administration two or three times daily. It is well accepted that patients' compliance with therapy tends to decrease as the dosage frequency increases and that regimens should be simplified as far as possible to support good compliance with therapy.[7]

Pharmacokinetic studies of the conventional immediate-release formulation of metformin have shown that this agent is absorbed into the upper gastrointestinal tract, with only minimal absorption occurring in the colon.[8] The principal side effects of standard metformin tablets are gastrointestinal in nature.[9] A double blind, parallel group dose–response trial in a total of 451 type 2 diabetic patients showed that the incidence of gastrointestinal side effects was approximately 20-30% in patients randomized to receive metformin 500-2500 mg/day.[10] Metformin extended release (MSR) has been formulated to address issues of GI tolerability and multiple daily dosing.[11] This newer formulation releases the active drug through hydrated polymers, which expand after uptake of fluid. This prolongs gastric residence time, which produces slower drug absorption in the upper gastrointestinal tract and allows once-daily dosing.[12] The low bioavailability and short half-life of metformin hydrochloride (MH) make the development of sustained-release forms desirable. However, drug absorption is limited to the upper gastrointestinal (GI) tract, thus requiring suitable delivery systems providing complete release during stomach-to-jejunum transit.[13]

A randomised, double-blind clinical trial demonstrated that patients with type 2 diabetes who had been receiving twice daily immediate-release metformin (MIR) achieved comparable glycaemic control when therapy was switched to once daily MSR at the same or a greater total daily dose.[14] Furthermore in a retrospective clinical review, patients switched from MIR to MSR experienced fewer gastrointestinal side effects on comparable doses of MSR.[15]

None of the studies report the effects of such sustained/extended/controlled release metformin in comparison with immediate release metformin on other cardiovascular risks like blood pressure and obesity associated with type 2 diabetes mellitus.

Hence, a present study was planned to compare the anti-diabetic efficacy of immediate release and a sustained release formulation of metformin as well as their effects on cardiovascular risk parameters like the lipid profile in diabetics using one of the sustained release preparations available in the Indian market and for which there are so far no published reports highlighting its metabolic effects.

METHODS

Study design and subjects

This study was a prospective, randomized double-blind, single centre study. The study was conducted in a tertiary care hospital where patients attending the medicine outpatient department (OPD)/diabetes clinic were recruited. The study protocol was submitted to the institutional ethics committee and approval was obtained. Written informed consent was obtained from all subjects.

Inclusion criteria were newly diagnosed cases (male/female) of diabetes mellitus type 2 (fasting blood glucose >126 mg% or 2-hr postprandial blood glucose >200 mg%) who as per the clinician, are deemed fit to receive metformin monotherapy. Whereas patients with age <18 years or >65 years of age, pregnant women, type 1 diabetics, severely symptomatic diabetes (fasting blood glucose more than 300mg% requiring polytherapy or insulin), patients with other cardiac, hepatic, renal comorbidities, and on the drugs that may affect glycaemic control (e.g. beta 2 agonists, phenytoin, thiazide/loop diuretics and glucocorticoids) were excluded from study.

Newly diagnosed cases were randomized to either metformin immediate release (MIR) group or metformin sustained release (MSR) group. 20 subjects were recruited in each group. MIR group was received 500mg of conventional metformin (MFD by: Ciron Drugs & Pharmaceuticals Pvt Limited) with morning meal at 12:00 Noon daily for 1 week followed by 500 mg of metformin twice daily with meals (12 Noon and 8:00 PM) from week 2 till the18 weeks. MSR group received 500mg sustained release metformin (MFD by: USV limited) with the evening meal at 8:00 pm for 1 week followed by 1000 mg sustained release metformin as a single dose with the evening meal at 8:00 pm from week 2 till 18 weeks.

Follow up visits

The subjects were followed up at 2 week intervals after randomization up to completion of 18 weeks. At each visit the compliance was confirmed by pill count.

Outcome measures

At visit 0 and last visit (at 18th week) body weight, waist circumference (at the level of umbilicus) and systolic and diastolic blood pressure was recorded using standard instruments. Similarly, at visit 0 and last visit blood was collected for estimation of fasting blood glucose and post prandial blood glucose with glucose-oxidase method, glycosylated haemoglobin (HbA1c) using TECHO diagnostics kit. Lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) using BIOLAB diagnostics kit. At each of the other fortnightly visits body weight, waist circumference (at the level of umbilicus) blood pressure was recorded. Blood was collected for estimation of fasting blood glucose.

At each visit the patients were enquired about the occurrence of adverse effects during the previous fortnight along with its severity and frequency. They

were also asked for any changes in any other medication that they may be receiving for co-existing illnesses (e.g. antihypertensive medication). In case of any adverse event or otherwise, the patient was free to withdraw from the study without giving any reason whatsoever.

Statistical analysis

Values were expressed as the mean±SD. Change and % change in fasting and post prandial blood glucose levels, glycosylated haemoglobin, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride in MSR group was compared with that in MIR group using unpaired-t test.

Change in weight, systolic and diastolic blood pressure, waist circumference, in MSR group was compared with that in MIR group using unpaired-t test.

Values within group at visit 0 and visit 9 are compared by paired-t test.

Number of patients who had achieved the target HbA1c value of 7% was compared between MSR and MIR group using chi-square test. Incidence of adverse effects reported by patients in MSR group was compared with that in MIR group using chi-square test.

$p < 0.05$ was considered to be significant.

RESULTS

General information and baseline data

A total of 40 subjects were enrolled in this study. Out of which, 20 subjects each were randomly assigned to metformin immediate release group (MIR) and metformin sustained release group (MSR). All 40 subjects enrolled in the study completed the study. Out of 40 patients 24 (60%) were males and 16 (40%) were females. Patients in both the groups were comparable with respect to baseline demographic data (age, sex, weight and waist circumference) and biochemical data (fasting blood glucose, postprandial blood glucose, HbA1c, and TC, LDL, HDL, TG) (Table 1).

Fasting blood glucose (FBG) level shows continuous decrease from baseline (visit 0) to visit 9 in both MIR and MSR groups. Statistically significant decrease ($p<0.05$) seen from visit 5 onwards in MIR group whereas from visit 2 onwards in MSR group. On comparing both groups at 18 weeks for fasting blood glucose; no significant difference is seen (Figure 1). Similarly, Post Prandial Blood Glucose level decreases significantly from baseline to visit 9 but no significant difference observed between two groups at the end of study.

Both MIR and MSR group showed statistically significant decrease in HbA1C. On comparing change i.e. Δ HbA1c (visit 9 HbA1C-visit 0 HbA1C) between 2 groups, no significant difference (p=0.78) observed (Figure 2).

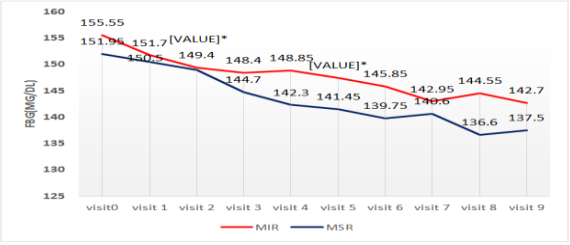
7 patients in MIR and 9 patients in MSR group achieved HbA1C American Diabetic Association (ADA) target of 7% at 18 weeks. On comparing 2 groups for ADA target of 7% by chi square test, no statistically significant difference is seen (p value 0.51) (Table 2).

Table 1: Distribution of baseline demographic and biochemical data for metformin immediate release (MIR) and metformin sustained released (MSR) groups (Mean± SD).

Groups	MIR Group (n=20)	MSR Group (n=20)
Age (yrs.')	53.95±8.02	53.83±7.83
Males' n (%)	11 (55%)	13 (65%)
Females' n (%)	9 (45%)	7 (35%)
Weight (kg)	74.60±14.87	76.25±9.71
Waist circumference (cm)	88.10±11.08	93.35±10.74
Height	162.65±8.99	162.36± 9.16
Fasting blood glucose (mg/dl)	155.55±21.52	151.95±19.23
Post prandial blood glucose (mg/dl)	228.10±32.24	225.25± 46.71
Total cholesterol (TC) (mg/dl)	190.95±23.44	193±17.42
LDL cholesterol (mg/dl)	124.65±23.68	130.45±21.02
HDL cholesterol (mg/dl)	36.25±10.77	34.65±9.68
Triglycerides (TG) (mg/dl)	133.60±13.03	135.55±17.42

Table 2: Number of subjects from MIR and MSR group who achieved American Diabetic Association target for HbA1c (7%).

	MIR (n= 20)	MSR (n= 20)
Achieved	7	9
Not achieved	13	11
Total	20	20



(* $p<0.05$)

Figure 1: Comparison between MIR and MSR group for fasting blood glucose (mg/dl) from baseline (visit 0) to last scheduled visit 9 (Mean ± SD).

Total cholesterol (TC), Low density lipoprotein (LDL), and triglycerides (TG) levels showed decrease in their values at 18 weeks as compared their baseline values, but no significant decrease was seen within and between the groups MIR and MSR namely. Whereas high density lipoprotein (HDL) level showed slight increase in MSR group at the end of study, but increase was not significant within and between groups (Table 3).

Table 3: Lipid profile (TC, LDL, HDL, and TG), obesity (weight, waist circumference) and blood pressure between MIR and MSR group (Mean±SD).

Parameters	MIR Group		MSR Group	
	Baseline value	End of study value	Baseline value	End of study value
TC (mg/dl)	190.95±23.44	187.20±22.46	193±17.42	191.80±17.56
LDL (mg/dl)	124.65±23.68	121.8±23.02	130.45±21.02	130.1±19.88
HDL (mg/dl)	36.25±10.77	35.75±10.61	34.65±9.68	36.65±10.12
TG (mg/dl)	133.60±13.03	132.45±13.06	135.55±17.42	133±14.60
Weight (KG)	74.6±14.87	73.17±15.28*	76.25±9.71	74.2±9.71*
Waist circumference (cm)	88.1±11.8	82.7±11.34*	93.35±10.47	86.8±10.35 *
Systolic blood pressure (mmHg)	129.4±5.95	128.5±4.04	128.6±4.59	128.1±3.07
Diastolic blood pressure (mmHg)	80.7±3.4	81.3±2.53	82.8±1.88	82.7±1.49

(* p<0.05)

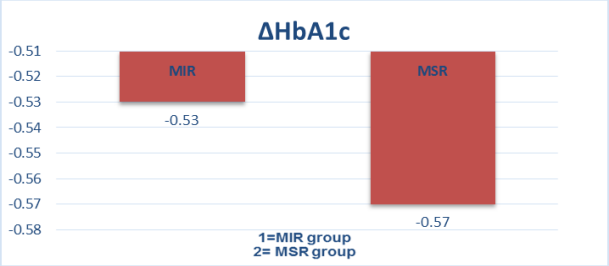


Figure 2: Δ HbA1c (visit 9-visit 0) between MIR and MSR group.

Both metformin formulation MIR and MSR showed statistically significant reduction in weight as compared to their baseline values. (*p<0.05). There was no statistically significant difference seen for change in weight (Δ weight = visit 9 - visit 0) in MIR and MSR group (p value 0.80) (Figure 3). Waist circumference also decreases significantly as compared to baseline value (*p<0.05) in both groups, but no statistically significant difference seen for change in waist circumference (Δ waist circumference = visit 9 - visit 0) in MIR and MSR group (p value 0.22). Present study did not show any effect on systolic and diastolic blood pressure (Table 3).

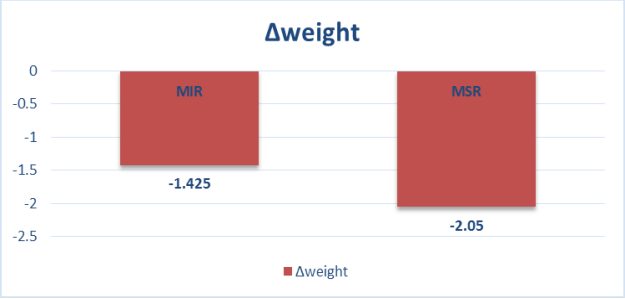


Figure 3: Δ weight (visit 9 weight – visit 0 weight) between MIR and MSR group.

Adverse events

The adverse effects were seen in both MIR and MSR groups. Total number of adverse events in MIR group were 8 (40%) and 4 (20%) in MSR group. Amongst all adverse events, nausea was the most common adverse effect, seen in 5 (12.5%) patients, 4 and 1 in each MIR and MSR group respectively. Diarrhoea is seen in 3 (7.5%) patients, with 2 and 1 in MIR and MSR group respectively, whereas abdominal discomfort seen in 4 (10%) patients, with 2 patients in each MIR and MSR group. On comparing between 2 groups by chi square test, no statistically significant difference is seen (P value 0.5) (Figure 4).

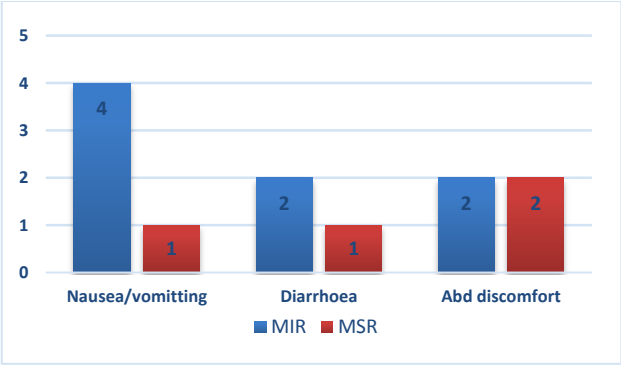


Figure 4: Adverse effects between MIR and MSR group.

DISCUSSION

Type 2 diabetes mellitus is a progressive disease in which a gradual loss of ß-cell mass and function underlies an on-going deterioration in glycaemic control that requires increasingly intensive treatment to achieve euglycaemia.[16,17] Good glycaemic control is crucial to

reduce the development and progression of micro vascular diseases such as retinopathy, nephropathy, neuropathy and macro vascular disease, which is the leading cause of premature death in patients with type 2 diabetes.[18-20] Metformin is recommended in International Guidelines as first line therapy due to its favourable profile on metabolic indices of glucose, lipid and weight control as well as offering protection from life threatening complications and premature mortality.[21]

Unfortunately metformin use is limited by gastrointestinal (GI) side effects, with up to 25% describing some form of GI upset. This leads to cessation of the drug in 5-10% of patients. The pharmacokinetics of metformin necessitates at least twice daily dosing. Poor GI tolerability and more than once daily dosing are likely to lead to reduced adherence to metformin in some people.[22]

An extended-release formulation of metformin may lead to improved tolerability, by smoothing the peaks and troughs in blood metformin concentrations and delaying the achievement of peak blood metformin concentrations, compared with an immediate-release formulation.[23] Hence, study was plan to undertake a study to compare the anti-diabetic efficacy of immediate release and a sustained release formulation of metformin as well as their effects on cardiovascular risk parameters like the lipid profile in diabetics using one of the sustained release preparations available in the Indian market and for which there are so far no published reports highlighting its metabolic effects.

Both metformin immediate release (MIR) and metformin sustained released (MSR) group showed statistically significant reduction in fasting blood glucose (FBG) at the end of study (18 weeks). Statistically significant difference is seen since from visit 6 onwards in MIR group, whereas significant difference seen from visits 2 onwards in MSR group. On comparing between 2 groups by unpaired t test, no statistically significant difference seen (p value 0.44). The results in present study matches with the study conducted by Sherwyn D et al[24] where all groups showed statistically significant reduction in FBG level, and significant reduction seen since visit 1 onwards. The reason for significant reduction in Sherwyn D et al. study since visit 1 could be higher dose 1500 mg of metformin used in all groups whereas in present study we used 1000 mg of metformin. A multi centric study conducted by Fujioka K et al[23] also showed comparable glycaemic control when patients were shifted from twice daily MIR 500 mg to once daily MSR 1000 mg or 1500 mg.

MIR and MSR group showed statistically significant reduction in post-prandial blood glucose (PPBG) at 18 weeks (p value<0.05). Comparison between 2 groups showed no significant difference (p value 0.4). Similar results were seen in study conducted by Bhansali A et al[25] which showed equal doses of 2 formulation MIR and MSR achieved comparable post prandial blood glucose level. However study conducted by Gao H et al[26] showed MSR given as a single evening dose of 1500 mg as compared to thrice daily doses of MIR 500 mg has weaker in reducing post prandial 120 min hyperglycaemia and that could be explained by the pharmacokinetic properties of MSR whose once daily dosing in the evening led to lower blood concentration of metformin in next morning than thrice daily dosing of MIR.

HbA1c values decreases significantly in both MIR and MSR group at 18 week (p value < 0.0001). On comparing between 2 groups by unpaired t test, no statistically significant difference seen (p value 0.14). Results in present study matches with a multicentric study conducted by Gao H et al[26] which showed modest but significant decrease from baseline mean HbA1c in both MIR and MSR groups after 12 weeks of treatment, however there was no significant difference in mean HbA1c values observed between 2 groups at the end of 12 weeks treatment (p value 0.73). Similarly studies conducted by Levy J et al[21] and Bhansali A et al[25] showed comparable glycaemic control when patients were switched from immediate release formulation to sustained release formulation. Present study showed no significant decrease after 18 weeks for either MIR or MSR group for lipid profile parameters like total cholesterol (TC), LDL cholesterol, HDL cholesterol and Triglycerides (TG). Similar findings were seen with a study conducted by Bhansali A[25] where switched from thrice daily immediate release formulation to once daily sustained released formulation at 3 months, showed no significant difference for TC, HDL, LDL and TG. A multicentric study conducted by Gao H et al[26] also showed no significant difference between any groups for lipid profile parameters.

In present study, weight decreased from 74.6 to 73.17 in MIR group and 76.25 to 74.2 in MSR group. Both group showed statistically significant reduction for weight (kg) at 18 weeks. But no significant difference is seen between 2 groups. Waist circumference (WC) decreases significantly (p<0.05) in both groups at the end of study. However, comparison between 2 groups did not show statistically significant difference (p=0.24). A 12 week randomized, open labelled, positive controlled multi centric study conducted by Gao H et al[26] showed significant reduction in metabolic parameters in both groups but no significance seen when 2 groups were compared, which is similar to findings from present study. Similarly one retrospective study conducted by Donnelly et al[22] and 6 month switched over study from MIR to MSR group conducted by Levy J et al[21] showed similar findings that metabolic parameters like weight and body mass index (BMI) showed no significant difference between MIR and MSR groups.

Both MIR and MSR groups did not show significant reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 18 weeks. These findings were similar with the findings of a Meta-analysis conducted by

Wulffele M et al[27] which showed no significant effect by metformin treated group as compared to control group in whom various hypoglycaemic agents were given.

In the present study, all the patients in both groups completed the study and tolerated the drug without any serious side effects. Incidence of adverse effects in MIR and MSR groups are 40% and 20% respectively. A multicentric, randomized, double blind parallel group study conducted by Fujioka K et al[23] also demonstrated that overall rate of treatment emergent clinical adverse drug experience was similar between 2 formulations. A double blind 24 week trial done by Sherwyn D et al[24] showed overall similar incidences in adverse effects between 2 groups, however fewer patients in sustained released group discontinued the treatment due to nausea in initial period than in immediate release group. The reason for discontinuation in immediate release group of Sherwyn D et al study could be higher dose of metformin (1500 mg) used.

To conclude, both metformin immediate release and sustained release formulations achieved comparable glycaemic control with reduction in obesity and without any effect on blood pressure and lipid profile. The present study showed sustained-release formulation would be as effective as immediate release formulation, with advantage of being reduce daily intake of total number of tablets.

Some limitations of the present study could be small sample size and small duration of study. Finally, as diabetes mellitus is a chronic disorder requiring lifelong treatment, a study of longer duration deserves to be carried out.

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