ORIGINAL ARTICLE

DOSE COMPARISON AND SIDE EFFECT PROFILE OF METFORMIN EXTENDED RELEASE VERSUS METFORMIN IMMEDIATE RELEASE

Maliha Hameed, Khurshid Khan, Sadia Salman, Nasir Mehmood

Endocrinology Department, Allama Iqbal Medical College, Jinnah Hospital, Lahore-Pakistan

Background: Diabetes Mellitus type 2 is very common worldwide, with majority of cases in Asia Pacific region. Metformin is the first line therapy, along with lifestyle modification for all type 2 diabetics as recommended by ADA. Metformin is available as conventional Metformin Immediate Release (MIR) and Metformin Extended Release (MXR). Metformin XR has better gastrointestinal tolerability and fewer side effects as compared to Metformin IR, with similar efficacy regarding anti-hyperglycaemic effects. The objective of this study was to determine whether metformin XR is as effective as Metformin IR in maintaining glycaemic control at equivalent doses or even at reduced doses; and to compare the side effect profile of the two preparations. **Methods:** This randomized control trial was conducted at Medical and Endocrinology OPD of Jinnah Hospital Lahore. A total of 90 type 2 diabetics of both genders were recruited using nonprobability purposive sampling. Patients were randomized into 3 groups; 30 in each group. Group 1 received Metformin IR 1000 mg twice daily; group 2 received metformin XR 1000mg twice daily; and group 3 received metformin XR 500 mg twice daily, for a period of three months. HbA1c was done at baseline and after three months of therapy along with fasting blood sugars and random blood sugars weekly. **Results:** The mean age of patients was 46±9 years, with 54% being males and 46% being females. There was a 1% reduction in HbA1c in group 1, 0.7% reduction in group 2 and only 0.4% reduction in group 3. Similarly, all three therapies were equally effective in reducing blood sugar fasting and blood sugar random at three months. Side effects namely diarrhoea, dyspepsia and flatulence were greatest with Metformin IR (40%) but less than half with Metformin XR at equivalent dose and negligible at half the dose. **Conclusions:** All three Metformin groups were effective in reduction of HbA1C and glycaemic control clinically and there is no statistical difference in HbA1c reduction among groups at three months.

Keywords: Diabetes Mellitus type 2, Metformin, Immediate release; Metformin extended release, Efficacy; Side effects

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes worldwide, accounting for 90% of cases.[1] An epidemic of T2DM is under way in both developed and developing countries, although the majority of cases are seen in non-European populations especially in Asia.[2–6] According to World Health Organization (WHO) the number of people with diabetes worldwide, 95% or more of who have T2DM, will double by 2030 and Asia Pacific countries, will bear the greatest burden.[3]

The management of diabetes Mellitus includes lifestyle intervention and pharmacotherapy. The available oral antihyperglycemic agents can be divided by mechanism of action into several groups: insulin sensitizers with primary action in the liver (Metformin), insulin sensitizers with primary action in peripheral tissues, insulin secretagogues, agents that slow the absorption of carbohydrates, insulins and agents that increase the activity of the incretin system.

Conventional metformin therapy with immediate-release formulations has been a mainstay of T2DM therapy for more than 30 years.[7,8] UKPDS shows that among overweight subjects, metformin not only improved microvascular complications similar to insulin and sulfonylurea but also demonstrated reduced rates of diabetes-related deaths and MI[1]. ADA has recently published a consensus statement that suggests initiation of metformin therapy in all patients with T2DM (without contraindications) at or near the time of diagnosis of diabetes.[1]

The precise mechanism of action of metformin is unknown; recent studies suggest that it activates AMPK, an intracellular signal of depleted cellular energy stores that stimulates skeletal muscle glucose uptake and inhibition of hepatic gluconeogenesis.[1]

Side effects of metformin mainly include gastrointestinal side effects like diarrhoea, dyspepsia, nausea and flatulence; it has no significant risk of hypoglycaemia; it is weight neutral and lactic acidosis is quite rare.[1] Chronic metformin use results in vitamin B12 deficiency in 30% of patients, after twelve to fifteen years of use. This may present without anaemia and as a peripheral neuropathy and

is often misdiagnosed as diabetic neuropathy. It can be arrested but not reversed with vitamin B12 replacement. Metformin is available in two formulations- Metformin immediate release (MIR) and Metformin extended release (MXR). MXR has better GI tolerability and fewer GI side effects as compared to MIR, proven by various studies, with a comparable or better efficacy regarding glycaemic control. MIR releases 90% of the drug within 30 min, with peak serum concentrations achieved within 3 h whereas MXR has longer gastric residence and is absorbed more slowly from the upper GI tract, with 90% release over 10 hours, which delays the time to peak concentrations by approximately 4–7 h. MXR delays time to peak metformin plasma concentrations, smooth plasma metformin peak and trough levels and leads to improved tolerability compared with MIR. A two-phase hydrophilic polymer matrix is used in the MXR, comprising an outer layer that hydrates to form a gel when exposed to fluid in the GI tract and a particulate inner phase from which metformin elutes gradually by diffusion over the dosing interval.[11] Pharmacokinetic studies show that MXR once-daily has comparable overall bioavailability to an equivalent twice-daily dose of MIR.[12,13]

Immediate-release metformin (MIR) is most effective at an average dose of approximately 2000 mg/day,[14] and has pharmacokinetic characteristics that typically require this to be divided between two or three smaller doses.[15] This has a negative impact on compliance and approximately 5% patients discontinue therapy due to side effects. By allowing once-daily administration, MXR has been demonstrated to significantly improve treatment adherence.[16] Clinical studies in patients with T2DM[17] have demonstrated that equivalent doses of MIR and MXR have similar anti-hyperglycaemic efficacy.

The objective of this study was to determine the efficacy and side effects of two doses of extended release metformin versus immediate release metformin; and to compare the side effect profile of the two preparations.

MATERIAL AND METHODS

A randomized control trial was done in Medical and endocrinology OPDs of Jinnah Hospital Lahore to evaluate the efficacy of immediate and extended release metformin. 90 Patients meeting inclusion criteria, i.e., newly diagnosed type 2 diabetics of either sex, not on metformin for the last 3 months and with no contraindications, were randomized into three groups. Group A was given metformin IR 1000 mg twice a day; group B received metformin XL 1000 mg twice a day; and group C received metformin XL 500 mg twice a day. Dose was gradually built to the required dose over a period of one month and then continued at the assigned dose for 12 weeks. Patients were instructed to monitor blood sugars at home; fasting thrice weekly on alternate days one week , then 2 hrs post meal sugars thrice weekly the next week, and so on. Patients were called for follow up every 2 weeks during the dose built up period, then every 4 weeks until the end of study. Blood glucose record was reviewed and side effect profile recorded. HbA1c was done at baseline and after completing three months of treatment. HbA1c was analysed by High Performance Liquid Chromatography. Data was entered and analysed in SPSS version 20.0 Mean and standard deviation was calculated for numerical variables like age, HbA1c, dosage. Frequency and %age was calculated for nominal variables like gender, side effects etc. ANOVA test was used for comparison between the groups.

RESULTS

A total of 90 patients were included in the study, 30 patients in each of the three groups. Mean age of patients was 46 years with a minimum age of 26 years and maximum age of 66 years. Regarding gender distribution, 54% of patients were male and 46% were female. In Group A, mean fasting blood glucose at the start was 166 with a standard deviation of 34; and at 3 months it was 136 with a standard deviation of 23. In Group B, mean bsf was 177 with a SD of 44 at the start; and 143 with a SD of 32 at 3months. In Group C, mean bsf was 163 with a SD of 37 at the start; and 143 with a SD of 32 after 3 months.

Blood sugar random (BSR) in group A was 224 with a SD of 43 at the start; and 176 with a SD of 18 at 3months. In group B, BSR was 204 with a SD of 51 at the start; and 182 with a SD 35 at 3 months. In group C, BSR was 198 with a SD 52 at the start; and 172 with a SD 42 at 3 months. HbA1c in group A was 7.4 with a SD 1.3 at the start and 6.4 with a SD 1.3 at 3 months. In group B HbA1c was 7.3 with a SD 1.5 at start and 6.6 with a SD of 1.4 at 3 months. In group C HbA1c was 6.5 with a SD of 1.2 at the start and 6.14 with a SD of 1.2 at 3 months. Analysis of variance (ANOVA) was used to assess statistical difference between the means among Blood sugar fasting, blood sugar random and HbA1c at start and three months of therapy. Significant difference between the means of HbA1c ($p<.05$) was found at start of therapy but no significant difference between the means were found among blood sugar fasting, blood sugar random and HbA1c at 3 month ($p>.05$), meaning all three therapies were equally effective.

Diarrhoea was experienced by 40.0% patients in group A, 10.0% in group B and 6.7% in group C ($p<.05$). Dyspepsia was experienced by 40.0% patients in group A, 20% in group B and 10% in group C ($p<.05$). Flatulence was experienced by 26.7% patients in group A, 10, 0% in group B and 6.7% in group C ($p>.05$). Neuropathy was insignificant in all three groups ($p>.05$).

Table-1: Case Summaries for age and BMI of subjects

Group		Age of Subjects	BMI of subjects
Metmorphin IR 1000	n	30	30
	Mean	45.60	25.796
	Std. Deviation	9.379	4.1250
	Minimum	26	19.4
	Maximum	62	35.4
Metmorphin XR 500	n	30	29
	Mean	46.63	27.134
	Std. Deviation	8.592	3.8856
	Minimum	34	20.0
	Maximum	65	33.9
Metmorphin XR 1000	n	30	30
	Mean	46.37	26.167
	Std. Deviation	9.722	4.8794
	Minimum	30	18.7
	Maximum	66	38.5

Table-2: Case summaries for blood sugar fasting, random and HbA1C at start and at 3 months of therapy.

Group		Blood Sugar Fasting at start	Blood Sugar Fasting 3 months	Blood Sugar Random at start	Blood Sugar Random 3 month	HBAc1 at start	HBAc1 at 3 months
Metmorphin IR 1000	n	30	30	30	30	30	30
	Mean	166.03	135.53	224.27	176.47	7.42	6.40
	SD	23.691	23.130	43.234	18.545	1.299	1.270
	Minimum	120	95	156	140	5	5
	Maximum	210	186	300	210	10	11
Metmorphin XR 500	n	30	30	30	30	30	30
	Mean	162.63	142.63	198.30	172.33	6.45	6.14
	SD	37.209	35.867	52.560	41.932	1.171	1.150
	Minimum	75	86	121	100	5	5
	Maximum	220	259	300	320	11	10
Metmorphin XR 1000	n	30	30	30	30	30	30
	Mean	177.53	143.17	204.13	182.60	7.32	6.64
	SD	44.532	31.690	51.333	35.906	1.533	1.420
	Minimum	96	77	145	130	5	5
	Maximum	265	220	339	280	10	10

Table-3: ANOVA for Blood sugar fasting, random and HbA1C at start and at 3 months of therapy.

		Sum of Squares	df	Mean Square	F	Sig.
Blood Sugar Fasting at start	Between Groups	3658.200	2	1829.100	1.397	.253
	Within Groups	113937.400	87	1309.625		
	Total	117595.600	89			
Blood Sugar Fasting 3 months	Between Groups	1089.622	2	544.811	.578	.563
	Within Groups	81946.600	87	941.915		
	Total	83036.222	89			
Blood Sugar Random at start	Between Groups	11136.467	2	5568.233	2.299	.106
	Within Groups	210737.633	87	2422.272		
	Total	221874.100	89			
Blood Sugar Random 3 month	Between Groups	1601.067	2	800.533	.708	.495
	Within Groups	98351.333	87	1130.475		
	Total	99952.400	89			
HBAc1 at start	Between Groups	17.099	2	8.549	4.742	.011
	Within Groups	156.850	87	1.803		
	Total	173.949	89			
HBAc1 at 3 months	Between Groups	3.702	2	1.851	1.121	.331
	Within Groups	143.606	87	1.651		
	Total	147.307	89			

Table-4: Side effects between groups:

	Group			
Side effects	Metmorphin IR 1000	Metmorphin XR 500	Metmorphin XR 1000	
Side effect 1: Diarrhoea	12	2	3	(X^2= 13.199 p= .001)
	40.0%	6.7%	10.0%	
Side effect: 2 Dyspepsia	12	3	6	(X^2= 7.826 p= .020)
	40.0%	10.0%	20.0%	
Side effect 3: Flatulence	8	2	3	(X^2= 5.574 p= .062)
	26.7%	6.7%	10.0%	
Side effect 4: neuropathy	3	2	2	(X^2= .310 p= .856)
	10.0%	6.7%	6.7%	
Total	43 (47.7 %)	11 (12.2%)	18 (20.0%)	

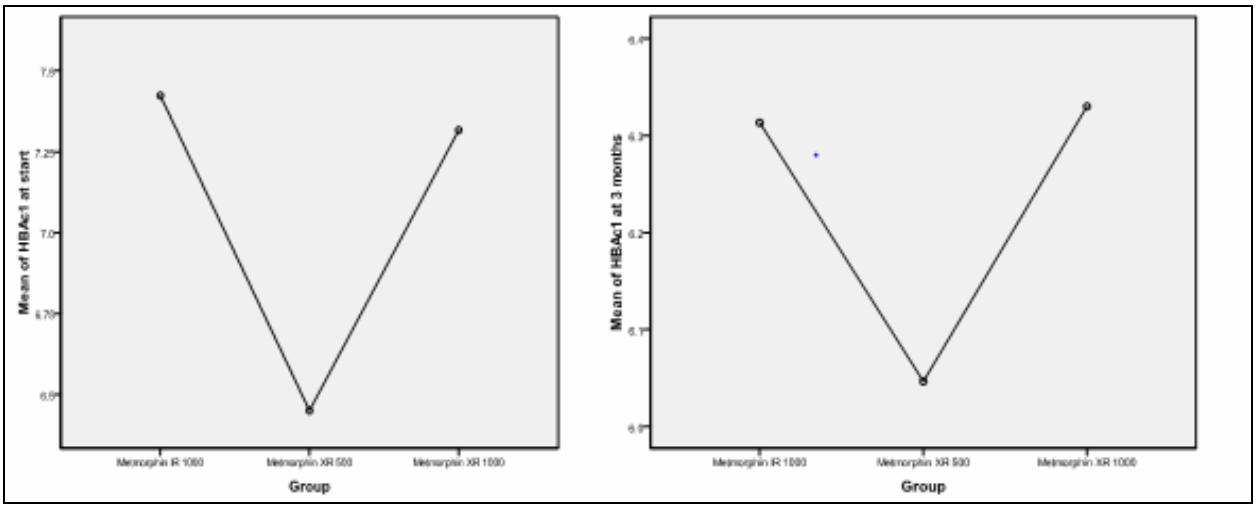

Figure-1: Mean HbA1c at start and after 3 months of therapy

DISCUSSION

Metformin has been the mainstay of therapy for type II diabetes mellitus for more than thirty years. It improves glycaemic control (1–1.5% reduction in HbA1c) which not only improves microvascular complications but also results in reduced rates of diabetes related deaths and myocardial infarction as demonstrated by various studies. ADA recommends metformin therapy in all patients with type II diabetes mellitus (unless contraindicated) at or near the time of diagnosis.

Metformin extended release is a formulation with better GI tolerability and fewer GI side effects as compared to Metformin immediate release, with a comparable or better efficacy regarding glycaemic control. To the best of our knowledge, our study is the first in Pakistan to compare efficacy and side effect profile of Metformin Immediate release versus Metformin extended release.

This is very important keeping in view the large burden of diabetes mellitus in our country. In the present study, mean age of patients was 46±9 years, with 54% being males and 46% being females. Patients were randomized into three groups, group A receiving MIR 1000mg twice daily, group B receiving MXR 1000mg twice daily and group C receiving MXR 500mg twice daily. HbA1c reduced from 7.4–6.4, i.e.,1% reduction in group A, 7.3–6.6, i.e., 0.7% reduction in group B and only 0.4% reduction in group C (6.5–6.1), but the difference between mean HbA1c reduction in all three groups was not statistically different (p>0.5) meaning all three therapies were equally effective. Similarly, BSF decreased from 166–136 in group A, 177–143 in group B and 163–143 in group C with a p-value > 0.5; and BSR decreased from 224–176 in group A, 204–182 in group B and 198–172 in group C at three months and all three therapies were equally effective.

This is similar to a study by Shwartz *et al* in adults with type 2 diabetes (newly diagnosed, treated with diet and exercise only, or previously treated with oral diabetic medications) in which patients were randomly assigned to receive one of three extended-release metformin treatment regimens or immediate-release metformin in a double-blind 24-week trial. Significant decreases (p<0.001) in mean HbA_{1c} (A1C) levels were observed by week 12 in all treatment groups. The mean changes from baseline to end point in the two groups given extended-release metformin (-0.73 and -0.74%) were not significantly different from the change in the immediate-release metformin group (-.70%), whereas the 2,000-mg extended-release metformin group showed a greater decrease in A1C (1.06%), with greater treatment adherence in extended release metformin groups.[18] Another study by Bhansali and Masoodi carried out in India also showed that patients with T2DM who had been receiving thrice-daily MIR achieved comparable glycaemic control when therapy was switched to once- or twice-daily MXR at the same total daily dose[19] in another Asian study by Kim Ch *et al* the mean change in HbA1c among patients treated with MXR was -0.8±0.9% from a mean baseline value of 8.0±1.4%. Regarding side effects, diarrhoea was experienced by 40% patients in group A, 10% in group B and 6.7% in group C. Dyspepsia was experienced by 40% patients in group A, 20% in group B and 10% in group C. Flatulence was experienced by 27% patients in group A, 10% in group B and 6.7% in group C which was statistically significant in all three groups (p<.05). Neuropathy was insignificant in all three groups (p>.05).

In a study by Kim Ch et al to assess the tolerability and antihyperglycemic efficacy of metformin XR in type 2 diabetics, conducted in six Asian countries, MXR appeared to be better tolerated than MIR and other oral anti-diabetic drug therapies. A considerably higher proportion of patients experienced

GI side-effects during MIR therapy (42.3%) than the MXR group (3.3%), of whom only 24 of the 3556 patients (0.7%) discontinued for this reason. The most common side-effects were diarrhoea (1.0%), dyspepsia (0.7%), nausea (0.6%), and flatulence (0.5%). These figures compare favourably with reported incidences of GI side-effects and related discontinuations in other studies of MXR.[7,9,10] The increased frequency of GI side effects in our population might be because of more unhygienic practices and an increased frequency of these problems in our population in general.

In a study by L Blonde in USA, the frequency of any GI adverse effect was 26.34% with MIR and 11.71 with MXR on comparable doses, i.e., less than half with MXR similar to our study.[9] Another study by Donelly LA *et al* in UK showed that adherence increased from 62% in the MIR group to 81% in MXR group (p<0.0001). [20]

CONCLUSION

All three Metformin groups were effective in reduction of HbA1C and glycemic control clinically and there is no statistical difference in HbA1c reduction among groups at three months.

AUTHORS' CONTRIBUTION

MH was the prime investigator and primarily carried out all the research including designing the research, designing *pro forma,* enrolling pts and following them; and writing the article. KK, incharge of the unit guided. NM and SS also assisted in enrolling patients.

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Address for Correspondence:
Dr Maliha Hameed, 430 Ravi Block, Allama Iqbal Town, Lahore-Pakistan
Email: maliha_jamshed@yahoo.com