WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 9, 529-537. Research Article ISSN 2277– 7105

# A COMPARATIVE STUDY ON THE SAFETY AND EFFICACY OF METFORMIN MONOTHERAPY AND METFORMIN-GLIMEPIRIDE COMBINATION THERAPY IN PATIENTS WITH TYPE-II DIABETES MELLITUS

**Mina Bhatta[*1], Amrit Khanal[2], Hari Prasad Sapkota[2] and Poonam Shah[1]**

[1]Shree Medical and Technical College, Bharatpur-12, Chitwan, Nepal.

[2]Scholars, Raghavendra Institute of Pharmaceutical Education and Research K. R. Palli Cross, Anantapuramu, Andhra Pradesh, India- 515721.

Article Received on
27 June 2017,
Revised on 17 July 2017,
Accepted on 07 Aug. 2017
DOI: 10.20959/wjpr20179-9179

***Corresponding Author**
**Mina Bhatta**
Shree Medical and Technical College, Bharatpur-12, Chitwan, Nepal.

## ABSTRACT

**Aim:** The aim of the study was to comparatively evaluate the efficacy of Metformin and Metformin-Glimepiride on glycemic control in patients with type-II Diabetes Mellitus. **Methodology:** A total of 184 subjects were included in the study and equally divided in to 2 groups of 92 subjects each i.e. monotherapy group and combination therapy group. The blood glucose level of subjects consecutively for three visits was recorded during two course of drugs intake with an interval of 2 weeks in between. **Results:** The fasting blood glucose and Post prandial blood glucose patients before and after monotherapy was 157.99±49.00, 248.60±80.8 and 128.95±35.3, 201.89±62.6. Similarly in combination therapy the fasting blood glucose and post prandial blood glucose before and after treatment was 169.13±43.9, 275.2±74 and 161.36±37.4, 247±39.37. **Conclusion:** Combination therapy with Metformin and Glimepiride has resulted in greater reduction of FBGL (P=0.021) in fasting condition and Metformin monotherapy has proven beneficial in lowering PPBGL (P=0.0013) in after food condition**.**

**KEYWORDS:** Metformin, Glimepiride, Hyperglycaemia, Blood Glucose Levels.

## INTRODUCTION

Diabetes mellitus is a metabolic disorder of carbohydrate, protein and fats.[1] Low and middle income countries face the greatest burden of diabetes mellitus.[2] It is one of the most

common chronic diseases in all countries, and continues to increase in numbers and significance, as changing lifestyles is leading to reduced physical activity, and increased obesity.[3]

Diabetes mellitus is a clinical syndrome characterized by metabolic defect resulting glycosuria, ketonemia hyperglycemia due to absolute or relative deficiency of Insulin.[4]

Pre-diabetes is more of a warning or an alert that if lifestyle changes do not occur such as increasing exercise, decreasing food portion sizes, weight loss, etc. the person will eventually end up getting Type 2 diabetes.[5] The Diabetes Society provides education services to those patients with pre-diabetes in order to assist them in adopting a healthier lifestyle. By changing habits and sticking to them, the person with pre-diabetes can usually prevent getting Type 2 diabetes or halt its progression for many years. A cure for DM has not yet been discovered. However, DM can be treated and controlled with diet, exercise, blood glucose monitoring and medication as needed.[6]

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% by 2030.[7] The prevalence of diabetes was more in women (22.04%) compare to men (16.06%).[8] Higher prevalence of diabetes in people staying in Sunsari district, eastern Nepal.[7] The prevalence of diabetes is increasing day by day in Nepal may be due to urbanization where there is more adherence towards scanty life. The prevalence of diabetes in urban area was higher in compare to the rural area.[9] Compared with subjects who have normal blood glucose levels, patients with type 2 diabetes have higher prevalence rates of MI (9.8% versus 1.8%), chest pain (9.5% versus 1.7%), coronary heart disease (9.1% versus 2.1 %), congestive heart failure (7.9% versus 1.1%), and stroke (6.6% versus 1.8%) respectively. A similar pattern was evident for microvascular complications, with higher rates of micro albuminuria (27.8% versus 6.1%) and foot problems, including amputation, foot lesions, and numbness (22.9% versus 10%) in patients with type 2 diabetes versus those with normal blood glucose, respectively.[10]

Various therapeutic agents are available for the management of DM but their use cannot be compromised with safety and efficacy.[11] So, the current work an attempt was made to justify the use of medication in management of DM.

## METHODOLOGY

It is a prospective, observational, unicentre study focusing on the evaluation of safety and efficacy of Metformin monotherpy with Metformin–Glimepiride combination therapy employed in the treatment of type-2 DM in the OPD of secondary care referral hospital of Nepal. Any experience of ADR, Side effects, and the value of blood glucose level (BGL) were considered as markers for the evaluation of safety and efficacy of the therapy. Many subjects who were interesting in joining the study were included by signing in the consent out of which about 184 participants were equally divided in to two groups of 92 participants in each group. Study participants were included basing on their BGL, age, co-morbidities whereas, pregnant women, patients with severe disease and those on other oral hypoglycemic agent were not included in the study.

During regular physician visit, patient's history including social history, habits, and hobbies, past medical and medication history was taken and patients meeting inclusion criteria were included in the study after obtaining their sign in written consent. Patient's blood glucose was recorded from pre designed patient profile form, from the Pathology Department. Patients were advised to take their medication and will be followed after every two weeks subsequently and their blood glucose level was recorded again from the patient profile form. Data regarding the experiences of adverse drug reactions (ADRs) experienced by the study subject was also recorded in the patient profile form based on the patient complaints during interview. The study was approved by Institutional Review/ethical board of Institute where the study was carried out with IRB no. SMTC/IRB/01/2012.

### Statistical analysis

Stastical analysis of the data in this study was carried out using SPSS version 17 and p value less than 0.05 is considered as statistically significant. All the information recorded in patients profile form were analyzed for various parameters like age, sex and ethnic distribution, patient's educational and occupational status, habitat, dietary habit by frequency and percentage, mean reduction in blood glucose level and the unwanted effect experienced by the patients within the study period.

## RESULT

55% of the males, between the age group of 61 years and above was identified to be suffering with DM, which co-incident with the research findings of Tanveen Kaurand *et al.*[12] MP Khapre *et al.*[13] Moreover Brahmins and Chhetri have predominated other races in case of

DM whereas, illiterate women, who are confined to the household works bearing food habits of non vegetarian were identified to be suffering from DM then educated and working women. Which yields similar results with that of the published work of MP Khapre *et al.*[13] and gray E. Fraser *et al.*[14] Majority of study subjects were non smokers, non alcoholics with actively participating in physical activities which support the work of Will JC *et al.*[15] and NP steyn *et al.*[16] but contradicted the findings of Ebenezer A. *et al.*[17]

**Mean reduction of Blood Glucose**

Before starting the treatment, the mean BGL of patients in fasting condition was 157.99 ± 49.00495 mg/dl and in post prandial state was 248.6 ± 80.879mg/dl. The mean reduction of BGL after two or four weeks of treatment by monotherapy (Metformin) and combination therapy (Metformin with Glimepiride) is given in table no. 1.

Thus, it was found that both therapeutic regimen significantly reduced BGL, in which, P value in Metformin monotherapy (both FBG and PPBG) after four weeks was (P=0.021, P=0.012), and in combination therapy (both FBG and PPBG) after four weeks was (P=0.001, P=0.001), as shown in table no.1. The mean reduction in BGL after four weeks is slightly more in combination therapy (FBG/PPBG-20.12 ± 14.55/-28.21 ± 34.7mg/dl) than monotherapy (-18.02 ± 6.11/-25.38 ± 16.35 mg/dl), which is supported by the study done by R.D. Shimphi and et.al in combination with Glimepiride and Glibenclamide on glycaemia control in patient with type-II DM was found that FBG and PPBG value were found to be reduced by (-54.59 ± 10.84 mg/dl) and (-92.09 ± 24.25 mg/dl) in each Metformin with Glimepiride and Metformin with Glibenclamide. The reduction in FBG in Metformin Glimepiride group was greater than (P: 0.001) than Metformin Glibenclamide group (P: 0.0066).[18]

The reduction of blood glucose by combination therapy after 2 and 4 weeks were significantly higher than by Metformin but the reduction was not consistent with combination therapy (Table no.1).

Thus various literatures supports that both Metformin combination with Glimepiride and Metformin monotherapy demonstrated a significant benefit for the treatment of type II diabetes mellitus. This justifies the hypothesis that Metformin combination and monotherapy are equally effective in reducing the BGL.

The details of Side Effect profile in monotherapy (Metformin) and combination (Metformin with Glimepiride) was found that number of side effects experienced by the patients on monotherapy (Metformin) were more than the patients with combination; where most of the patients suffered from nausea and vomiting 54% and 36% in mono and combination therapy respectively. Blurred vision was almost similar in both therapies.

Whereas, weight gain was more in case of combination therapy (24%) similar study done by Mellisa T. Fose and *et.al* side effects like, diarrhoea (53.2% and 11.7%), nausea vomiting (25.5% and 8.3%), flatulence (12.1% and 5.5%), abdominal discomfort (6.4% and4.8%), headache (5.7%and 4.8) were seen in monotherapy and combination therapy respectively.[16]

**Table no. 1: Mean reduction in Blood Glucose level**

| Medicine | Mean(mg/dl) | | F | P |
|---|---|---|---|---|
| MMFBG | $F_0$=146.97±51.47 | $F_0$-$F_2$=5.00±4.96 | 3.88112 | 0.021763 |
| | $F_2$=141.97±46.51 | $F_2$-$F_4$=13.02±11.15 | | |
| | $F_4$=128.95±35.36 | $F_0$-$F_4$=18.02±16.11 | | |
| MMPPBG | $PP_0$=227.27±79.041 | $PP_0$-$PP_2$=10.28±10.957 | 2.120377 | 0.121937 |
| | $PP_2$=216.99±68.084 | $PP_2$-$PP_4$=15.1±5.394 | | |
| | $PP_4$=201.89±62.69 | $PP_0$-$PP_4$=25.38±16.35 | | |
| CFBG | $F_0$=169.13±43.902 | $F_0$-$F_2$=7.7±6.442 | 6.781 | 0.001336 |
| | $F_2$=161.36±37.46 | $F_2$-$F_4$=12.35±8.11 | | |
| | $F_4$=149.01±29.35 | $F_0$-$F_4$=20.12±14.55 | | |
| CPPBG | $PP_0$=275.21±74.07 | $PP_0$-$PP_2$=3.55±19.52 | 6.503786 | 0.00174 |
| | $PP_2$=271.66±54.55 | $PP_2$-$PP_4$=24.66±15.18 | | |
| | $PP_4$=247.00±39.37 | $PP_0$-$PP_4$=28.21±34.7 | | |

Where; MMFBG= With Metformin monotherapy, fasting blood glucose; MMPPBG= With Metformin monotherapy, post prandial blood glucose; CFBG= With Combination therapy, fasting blood glucose; CPPBG=With Combination therapy, post prandial blood glucose; $F_0$= Fasting BGL on first visit; $F_2$=Fasting BGL after two weeks; $F_4$= Fasting BGL after four weeks; $PP_0$= Post prandial BGL on first visit; $PP_2$= Post prandial BGL after two weeks; $PP_4$= Post prandial BGL after four weeks

**Table no. 2A and 2B: Statistical Analysis: One way ANOVA, Reduction of BGL with Combination therapy [2A] & Monotherapy [2B]**

| | Fasting | | | Post prandial | | |
|---|---|---|---|---|---|---|
| **Source of Variance** | **Within sample** | **Between sample** | **Total** | **Within sample** | **Between sample** | **Total** |
| SS | 381547 | 18955.04 | 400502 | 911176.8 | 43414 | 954591.4 |
| d. f | 273 | 2 | 275 | 273 | 2 | 275 |
| MS | 1397.608 | 9477.521 | | 3337.644 | 21707.32 | |
| F | 6.781 | | | 6.503786 | | |
| P | 0.001336 | | | 0.00174 | | |

**[2A]**

| | Fasting | | | Post prandial | | |
|---|---|---|---|---|---|---|
| **Source of Variance** | **Within sample** | **Between sample** | **Total** | **Within sample** | **Between sample** | **Total** |
| SS | 557893.2 | 15690.2 | 573583.4 | 1362867.48 | 20904.52 | 1383808 |
| d. f | 276 | 2 | 278 | 276 | 2 | 278 |
| MS | 2021.352 | 7845.11 | | 4937.925 | 10470.26 | |
| F | 3.88112 | | | 2.120377 | | |
| P | 0.021763 | | | 0.121937 | | |

**[2B]**

## DISCUSSION

A total of 184 study participants (92 receiving Metformin monotherapy and 92 receiving Metformin combination therapies) were enrolled in the study. These patients were followed for 4 weeks and their BGL and side effects were recorded at 0, 2 and 4 weeks of interval. Data obtained from the patients was entered in the patient profile form designed for the study and were analyzed using SPSS version 17.

During the study it has been found that type II DM effected males (65%) were more when compared to female (35%) The aim of our study was to compare the effect on glycemic control in patient and mostly it was pronounced at the age above 60 years. The occurrence of diabetes was greater in non-vegetarian (86%) people than vegetarian (14%) people. Also, it was noticed that the literate people were more pronounced to DM while the housewife (58%) were more liable to DM. It may be attributed to the fect that females are confined to the household work, lead more sedentary life that the working one. However, non- vegetarian the lipid profile may be increased when compared to vegetarian and during the old age most of the enzymatic process starts getting deteriorated.

Indeed, Metformin-Glimepiride combination therapy produced greater mean changes from the baseline in case of fasting blood glucose and post prandial blood glucose (20.12 ± 14.552mg/dl and 28.21 ± 34.7mg/dl) for Metformin monotherapy (Group I) it was (18.02 ± 16.11mg/dl and 25.38 ± 16.35mg/dl). The statistical analysis using one way ANOVA concludes that the combination therapy reduced FBG and PPBG are more significantly (P-0.001336 and P-0.00174) than monotherapy (P-0.02763 and P-0.121937) respectively.

These results demonstrate that treatment with Metformin-Glimepiride was more efficacious than with Metformin monotherapy in improving glycaemia by achieving therapeutic goals for FBG and PPBG in patients with type 2 diabetes. At the interval of every two weeks for three visits of each patient, the significant reduction in blood glucose were found in both groups but the patients treated with Metformin combined with Glimepiride resulted in significantly greater reduction indicated by P value for fasting as Metformin monotherapy (0.021763) is greater than Metformin Glimepiride combination therapy(0.001336) and P value for post prandial for Metformin monotherapy (0.121937) is greater than Metformin Glimepiride combination therapy(0.00174).

Also more side effects were observed in Metformin monotherapy than combination (Metformin with Glimepiride). The observed side effects were Nausea and vomiting, fatigue, Metallic taste, Allergic reactions, blurred vision, weight gain and Myalgia were found in monotherapy and combination as (54% and 36 %), (1% and 2%), (3% and 2%), (1% and 4%), (29% and 28%), (6% and 4%) respectively. Combination therapy was more effective which can be observed as mean reduction of blood glucose in fasting with monotherpy (139.296 ± 44.446) and with combination therapy (159.83 ± 36.904) and mean reduction of blood glucose in post prandial with monotherapy (215.303 ± 69.938) and with combination (264.623 ± 55.996).

From the assumption described in results and discussion the present study concludes that the combination Metformin-Glimepiride and Metformin monotherapy reduced the Fasting and post-prandial blood glucose significantly. But the Metformin-Glimepiride combination provided superior control of glycaemia as compare to the Metformin monotherapy. Also the adverse effects were seen more in monotherapy than combination therapy. So the Metformin-Glimepiride combination can be considered as the best in patients with increased BGL. However, monotherapy was identified to be cost effective than combination therapy.

**Recommendation**

Though both monotherapy and combination therapy were found effective in reducing BGL, prescribers are recommended to monitor the patients on Metformin for side effects and counsel them about such problems and to improve the adherence. However, further studies in large number of patients covering different regions of sub continent are needed to extrapolate these findings. We also recommend that the design of such study should include effects from the non-pharmacological treatment and patients should be followed for longer time to obtain the long-term effects of drugs in terms of safety and efficacy.

**ACKNOWLEDGEMENT**

All the authors of the study are highly thankful to all the people who are directly and indirectly involved in the study making it a successful one.

**REFERENCES**

1. Garg A, Bonanome A, Grundy SM, Zhang Z-J, Unger RH. Comparison of a high-carbohydrate diet with a high-monounsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. New England Journal of Medicine, 1988; 319(13): 829-34.
2. Ramachandran A, Snehalatha C, Viswanathan V. Burden of type 2 diabetes and its complications-the Indian scenario. current science-Bangalore, 2002; 83(12): 1471-6.
3. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. Jama, 2002; 288(14): 1723-7.
4. Mellitus D. Diagnosis and classification of diabetes mellitus. Diabetes care. 2005;28:S37.
5. Li M, Zeng T, Liu R, Chen L. Detecting tissue-specific early warning signals for complex diseases based on dynamical network biomarkers: study of type 2 diabetes by cross-tissue analysis. Briefings in bioinformatics, 2014; 15(2): 229-43.
6. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. The Lancet, 2001; 358(9277): 221-9.
7. Mehta K, Karki P, Lamsal M, Paudel I, Majhi S, Das B, et al. Hyperglycemia, glucose intolerance, hypertension and socioeconomic position in eastern Nepal. Southeast Asian Journal of Tropical Medicine and Public Health, 2011; 42(1): 197.
8. Singh D, Bhattarai M. High prevalence of diabetes and impaired fasting glycaemia in urban Nepal. Diabetic medicine, 2003; 20(2): 170-1.
9. Dulal RK, Karki S. Disease management programme for Diabetes mellitus in Nepal. Journal of Nepal Medical Association, 2009; 48(176).

10. Edelman S, Henry R. Diagnosis and Management of Type 2 Diabetes. West Islip, NY: Professional Communications. Inc, 2007.
11. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care, 2009; 32(1): 193-203.
12. Kaur T, Bishnoi D. Effect of Sex on prevalence of Type 2 diabetes mellitus (T2DM) with respect to blood pressure, BMI and WHR among Punjabi population. International Journal of Medicine and Medical Sciences, 2010; 2(9): 263-70.
13. Khapre M, Mudey A, Goyal R, Wagh V. International Journal of Biological & Medical Research. Int J Biol Med Res, 2011; 2(3): 627-30.
14. Fraser GE, Lindsted KD, Beeson WL. Effect of Risk Factor Values on Lifetime Risk of and Age at First Coronary Event The Adventist Health Study. American Journal of Epidemiology, 1995; 142(7): 746-58.
15. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. International Journal of Epidemiology, 2001; 30(3): 540-6.
16. Steyn NP, Mann J, Bennett P, Temple N, Zimmet P, Tuomilehto J, et al. Diet, nutrition and the prevention of type 2 diabetes. Public health nutrition, 2004; 7(1a): 147-65.
17. Nyenwe EA, Odia OJ, Ihekwaba AE, Ojule A, Babatunde S. Type 2 diabetes in adult Nigerians: a study of its prevalence and risk factors in Port Harcourt, Nigeria. Diabetes research and clinical practice, 2003; 62(3): 177-85.
18. Shimpi R, Patil P, Kuchake V, Ingle P, Surana S, Dighore P. Comparison of effect of metformin in combination with glimepiride and glibenclamide on glycaemic control in patient with type 2 diabetes mellitus. Int J PharTech Res., 2009; 1: 50-61.