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Original Article

A COMPARATIVE STUDY TO ASSESS THE SAFETY AND EFFICACY OF SOME ORAL TRIPLE THERAPY REGIMENS IN PATIENTS WITH UNCONTROLLED TYPE 2 DIABETES MELLITUS

LAVANYA G.[1], MAKARANDH A.[1*], VENKATESHWARLU E.[1], SHARAVANABHAVA B. S.[1], SATHYANARAYANA K.[2]

[1]Department of Clinical Pharmacy and Pharm. D., Vaagdevi college of Pharmacy, MGM Hospital, Hanamkonda, Warangal, Telangana, India.[2]Satyam's Diabetes Hospital and Research Centre, Hanamkonda, Warangal, Telangana, India
[*]Corresponding author: Makarandh A.; [*]Email: sagarmakarandh@gmail.com

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ABSTRACT

Objective: This study evaluated the safety and efficacy of oral triple therapies (Sitagliptin (S)+Dapagliflozin (D), Vildagliptin (V)+Dapagliflozin (D), Gliclazide (GL)+Vildagliptin (V), Glimepiride (GP)+Vildagliptin (V), Glimepiride (GP)+Voglibose (VG)) as add-ons to Metformin (M) in inadequately controlled Type 2 Diabetes Mellitus (T_2DM) patients on dual therapy.

Methods: This prospective, observational, comparative and multi-centric study was conducted on 813 patients with T_2DM. The effect of therapy on glycaemic control in 813 patients were assessed using appropriate statistical analysis before treatment and at 3 and 6 mo post-treatment.

Results: All the parameters [Glycated Haemoglobin (HbA_{1C}), Fasting Blood Sugar (FBS) and Post Lunch Blood Sugar (PLBS)] were evaluated before the treatment and reassessed 3 mo and 6 mo after treatment. Average HbA_{1C} levels at baseline were 8.3±1.23, decreasing to 7.8±1.11 at 3 mo and 7.62±1.01 at 6 mo for M+GL+V, with significant differences ($p<0.0017$ and $p<0.0001$). For M+GP+V, HbA_{1C} decreased from 9.12±0.8 to 8.5±0.7 and 8.1±0.7 ($p<0.0001$). M+GP+VG showed a reduction from 8.98±0.88 to 8.57±0.82 and 8.17±0.75 ($p<0.0001$). M+V+D demonstrated a drop from 9.33±0.98 to 7.98±0.80 and 7.13±0.6 ($p<0.0001$), while M+S+D showed reductions from 9.35±0.67 to 7.77±0.62 and 6.78±0.47 ($p<0.0001$). FBS and PLBS decreased significantly across all combinations. For M+S+D and M+V+D, the incidence of hypoglycaemia, dizziness, and weight gain was lower compared to other combinations.

Conclusion: M+S+D and M+V+D were most effective in controlling glucose levels, indicating a favourable safety profile and improved glycaemic control in T_2DM patients.

Keywords: Dapagliflozin, Glimepiride, Gliclazide, Metformin, Sitagliptin, Type 2 diabetes mellitus, Vildagliptin

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INTRODUCTION

Diabetes Mellitus is a group of metabolic disorders characterized by chronic hyperglycemia due to deficiency of insulin secretion and/or resistance to insulin action. The chronic hyperglycemia of diabetes is associated with metabolic abnormalities in carbohydrates, lipids, and proteins, which results in long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (long-term complications of diabetes, which include microvascular, macrovascular, and neuropathic disorders) [1, 2].

The recommended initial T_2DM management approach includes lifestyle changes and monotherapy (usually with Metformin). If the HbA_{1C} goal has not been met with in approximately 3 mo of starting initial therapy, treatment should be intensified by adding a second agent; consider one of the five treatment options combined with Metformin: Sulfonylurea (SU), Thiazolidinedione (TZD), Dipeptidyl Peptidase (DPP-4) inhibitor, Sodium Glucose Co-transporter (SGLT2) inhibitor and 2 injectable agents Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) or Basal insulin. Glycaemic control should be reassessed again approximately 3 mo, and triple therapy should be considered if the HbA_{1C} target is still not achieved, combination injectable therapy, including basal insulin may be considered to be obtain glycaemic control. In patients with high baseline HbA_{1C} levels, initial treatment with dual-combination therapy can be considered. The AACE/ACE suggests initial dual therapy (i. e., Metformin plus another agent in addition to lifestyle therapy) for patients with an entry HbA_{1C} levels ≥7.5%, whereas the ADA suggests considering initial dual therapy if the entry HbA_{1C} is ≤9% [3].

The main aim of this study is to compare the safety and efficacy of oral triple therapy regimens (Sitagliptin (S)+Dapagliflozin (D), Vildagliptin (V)+Dapagliflozin (D), Gliclazide (GL)+Vildagliptin (V), Glimepiride (GP)+Vildagliptin (V), Glimepiride (GP)+Voglibose (VG)) as add-ons to Metformin (M) in patients with uncontrolled T_2DM.

MATERIALS AND METHODS

Study design

It was a Prospective, Observational, Comparative and Multi-centric study to be conducted in MGM Hospital, Dr. Satyam's Diabetes Hospital and Research Centre, Hanamkonda, Samraksha Diabetes, Thyroid and Endocrine Centre, Hanamkonda.

An approval was obtained prior to the study from the Institutional Human Ethics Committee. The approval number was "KIEC-2023/Pharm D-2018/Project-06" and informed consent was obtained from each patient after having been informed of all the aspects relevant to the study in their local language.

Study duration: 6 Month

Inclusion criteria

Inclusion criteria were patients who were willing to participate and submit the informed consent form, Age group 18 y or older with uncontrolled T_2DM with Metformin, Patients who were receiving Dapagliflozin and Sitagliptin or Dapagliflozin and Vildagliptin or Gliclazide and Vildagliptin or Glimepiride and Vildagliptin or Glimepiride and Voglibose along with Metformin.

Exclusion criteria

Exclusion criteria included Pregnant (Gestational Diabetes) or lactating women with Diabetes Mellitus, Patients of age group 17 y or younger, with Type 1 Diabetes Mellitus, with *denovo* Diabetes Mellitus, Patients presenting with moderate to severe renal

insufficiency [4], who were already diagnosed with Diabetic complications like Diabetic Neuropathy, Diabetic Nephropathy etc., patients receiving insulin as an add on therapy to Metformin, patients not willing to participate in the study, patients unwilling to disclose the information.

Parameters assessed

FBS, PLBS and HbA_{1C} values were assessed once in every 3 mo during the treatment. Primary endpoint was change in HbA_{1C}, FBS, and PLBS levels at 12 w (3 mo) and 24 w (6 mo) as compared to the baseline levels in all five groups.

RESULTS

Statistical analysis

All the parameters were expressed as Mean±Standard Deviation (SD). Data analysis was performed using MS Excel and Graph Pad Prism 9.5.1 Version. Statistical analysis was performed using ANOVA one-way method followed by Tukey's multiple comparison test to assess the significant difference between the efficacy parameters pre and post-add-on treatment.

A P value of <0.005 was considered statistically significant.

Table 1: Gender distribution of study subjects

Gender	No. of subjects (n=813)	Percentage
Female	424	52%
Male	389	48%

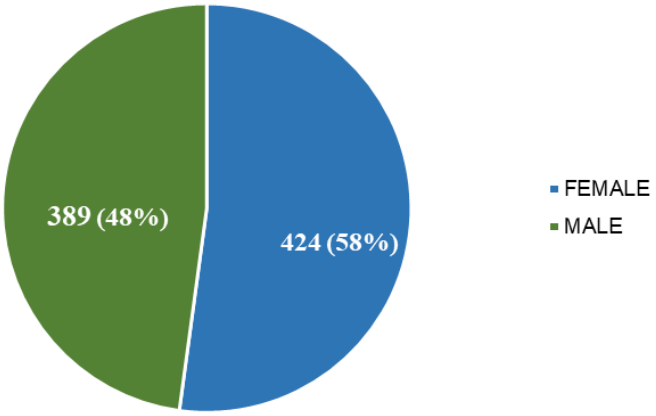


Fig. 1: Graphical representation on gender distribution of the study subjects

Table 2: Age distribution of study subjects

Age criteria	No. of subjects (n=813)
20-29	4
30-39	67
40-49	186
50-59	281
60-69	193
70-79	72
80-89	10

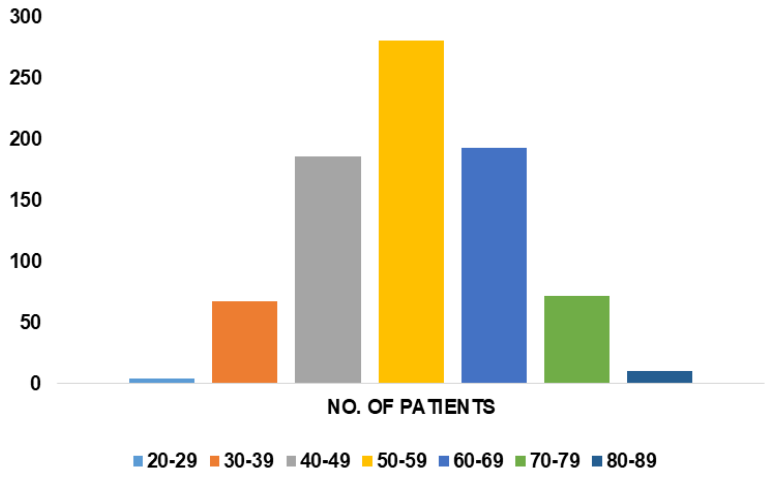


Fig. 2: Graphical representation on age distribution of the study subject

Table 3: Distribution of body mass index among study subjects

BMI classification	No. of subjects (n=813)
Underweight (Below 18.5)	22(3%)
Normal weight (18.5-24.9)	244(30%)
Overweight (25.0-29.9)	370(46%)
Obesity class-I (30.0-34.9)	134(16%)
Obesity class-II (35.0-39.9)	32(4%)
Obesity class-III (Above 40)	11(1%)

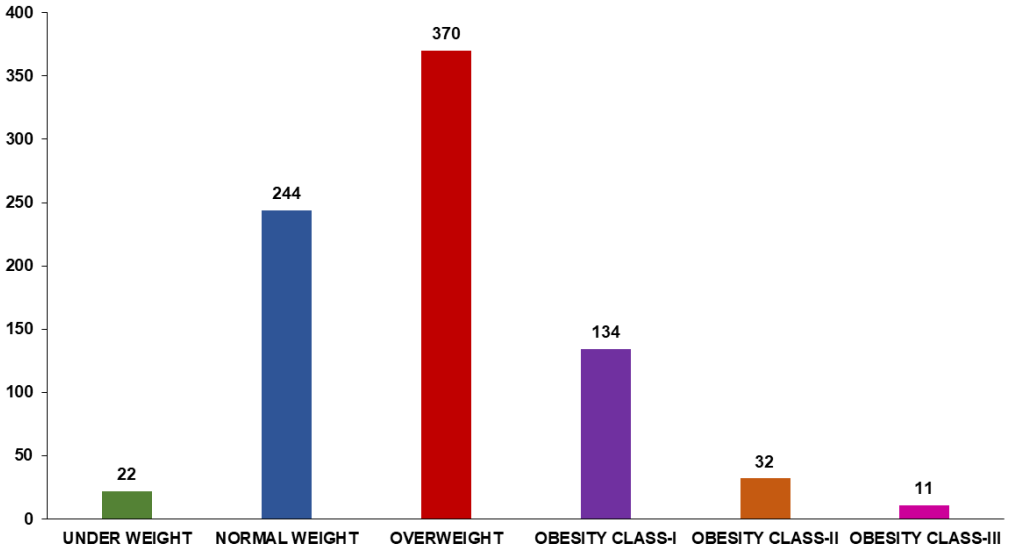


Fig. 3: Graphical representation on distribution of body mass index among study subjects

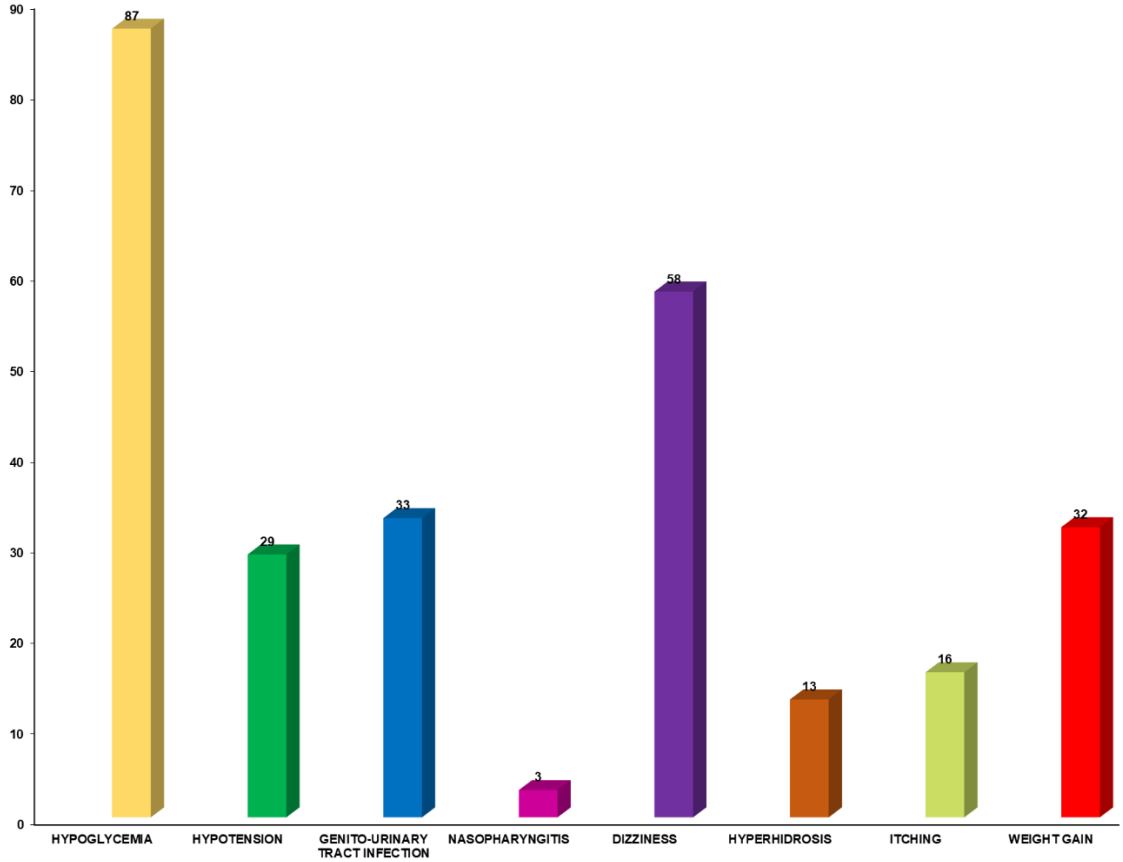


Fig. 4: Graphical representation on observed ADRs among study subjects

Table 4: Observed ADRs among study subjects

Safety parameters	No. of subjects (n=813)
Hypoglycemia	87(32%)
Hypotension	29(11%)
Genito-Urinary tract infection	33(12%)
Nasopharyngitis	3(1%)
Dizziness	58(21%)
Hyperhidrosis	13(5%)
Itching	16(6%)
Weight gain	32(12%)

Table 5: Safety parameters of M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups

Safety parameters	M+GL+V (n=123)	M+GP+V(n=228)	M+GP+VG (n=157)	M+V+D (n=210)	M+S+D (n=95)	Total
Hypoglycemia	28	27	21	8	3	87
Hypotension	4	11	2	7	5	29
Genito-urinary tract infection	1	4	1	16	11	33
Nasopharyngitis	3	0	0	0	0	3
Dizziness	14	16	15	8	5	58
Hyperhidrosis	4	3	3	1	2	13
Itching	5	5	4	2	0	16
Weight gain	13	11	4	2	2	32
Total	72	77	50	44	28	271

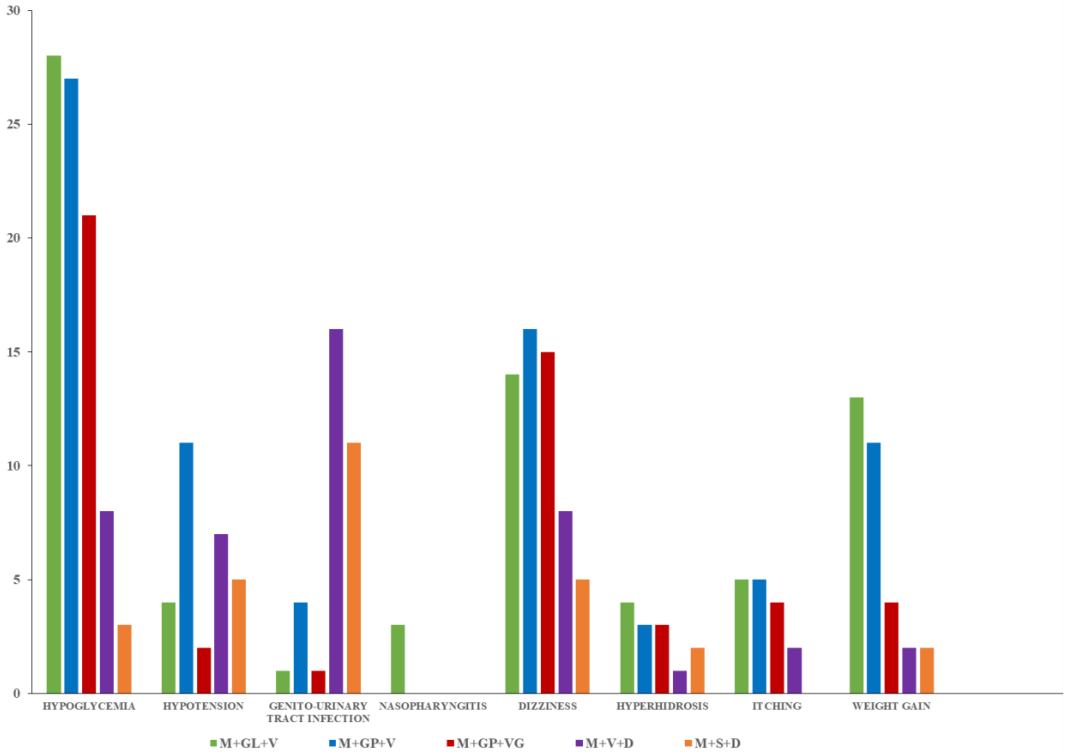


Fig. 5: Cumulative graphical representation on safety parameters of M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups

Table 6: Comparison of FBS levels among M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups

Drugs	Mean±SD visit-1	Mean±SD visit-2	Mean±SD visit-3	P-value V1-V2	P-value V1-V3	Average reduction % V1-V2	Average reduction % V1-V3
M+GL+V (n= 123)	154.83±49.54	133.15±44.97	124.0±39.12	***0.0005	****<0.0001	14%	20%
M+GP+V (n= 228)	176.56±53.31	144.51±33.67	119.32±21.63	****<0.0001	****<0.0001	18%	32%
M+GP+VG (n= 157)	179.17±63.0	147.43±41.61	123.01±28.16	****<0.0001	****<0.0001	18%	31%
M+V+D (n= 210)	190.78±54.61	143.22±36.21	113.12±22.24	****<0.0001	****<0.0001	25%	41%
M+S+D (n=95)	190.63±47.911	132.37±28.58	100.97±17.15	****<0.0001	****<0.0001	30%	47%

M= Metformin, GL= Gliclazide, GP= Glimepiride, VG= Voglibose, V= Vildagliptin, S= Sitagliptin, and D= Dapagliflozin, Mean±SD: Represents the Average±Standard Deviation of FBS levels measured at each visit. Visit-1, Visit-2, Visit-3: Measurements taken at baseline, 3 mo, and 6 mo post-treatment, respectively. P-Value: Statistical significance of changes between visits, determined by one-way ANOVA. ****<0.0001 indicates very high statistical significance. Average reduction % V1-V2 and V1-V3 = The percentage reduction in FBS levels from Visit-1 to Visit-2 and Visit-1 to Visit-3, respectively, indicates the treatment's effect over time.

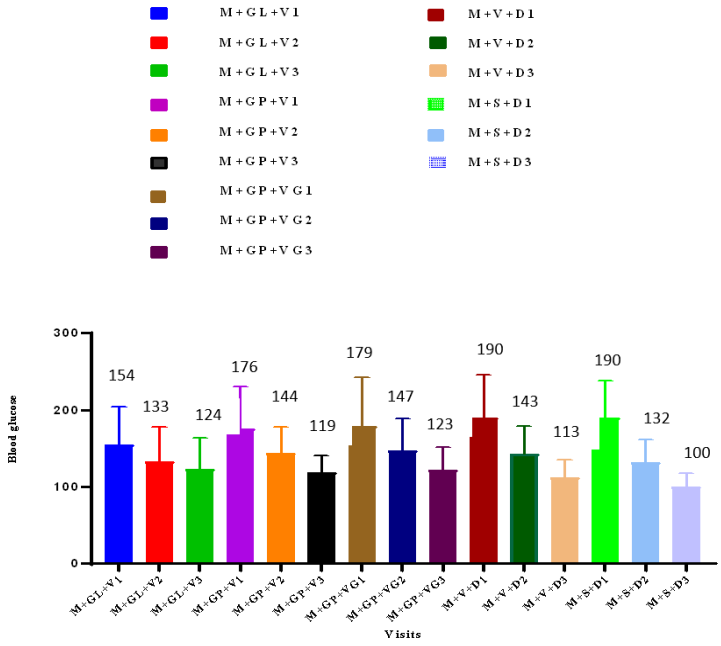
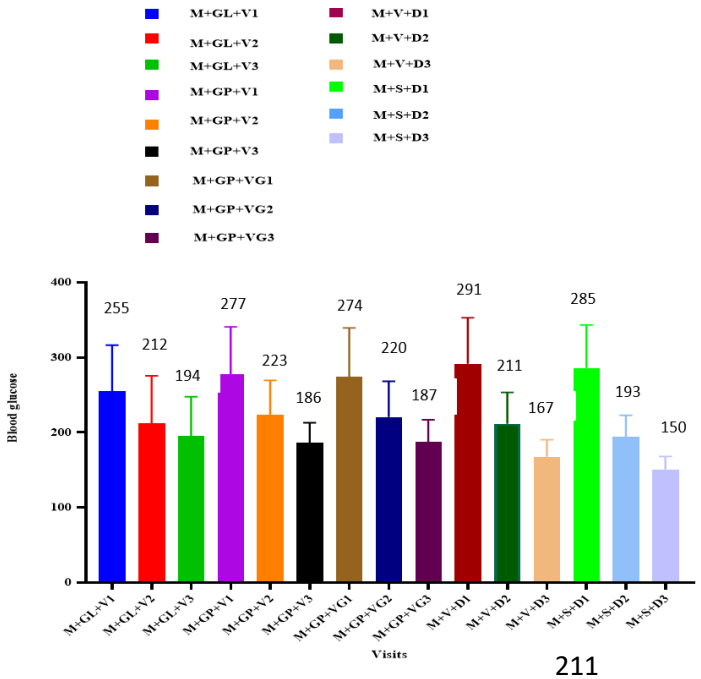


Fig. 6: Cumulative graphical representation of M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups FBS levels

Table 7: Comparison of PLBS levels among M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups

Drugs	Mean±SD visit-1	Mean±SD visit-2	Mean±SD visit-3	P-Value V1-V2	P-Value V1-V3	Average reduction % V1-V2	Average reduction % V1-V3
M+GL+V (n= 123)	255.15±61.07	212.3±63.09	194.9±52.49	****<0.0001	****<0.0001	17%	23%
M+GP+V (n=228)	277.744±62.83	223.61±45.78	186.0±26.88	****<0.0001	****<0.0001	19%	33%
M+GP+VG (n=157)	274.312±64.81	220.43±47.71	187.36±29.41	****<0.0001	****<0.0001	20%	32%
M+V+D (n=210)	291.54±61.28	211.55±41.77	167.42±22.84	****<0.0001	****<0.0001	27%	43%
M+S+D (n=95)	285.9±57.341	193.62±29.097	150.64±17.42	****<0.0001	****<0.0001	32%	47%

Mean±SD: Represents the Average±Standard Deviation of PLBS levels measured at each visit. Visit-1, Visit-2, Visit-3: Measurements taken at baseline, 3 mo, and 6 mo post-treatment, respectively. P-Value: Statistical significance of changes between visits, determined by one-way ANOVA. ****<0.0001 indicates very high statistical significance. Average reduction % V1-V2, V1-V3: The percentage reduction in PLBS levels from Visit-1 to Visit-2 and Visit-1 to Visit-3, indicates treatment effects over time.



211

Fig. 7: Cumulative graphical representation of M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups PLBS levels

Table 8: Comparison of HbA_{1C} levels among M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups

Drugs	Mean±SD visit-1	Mean±SD visit-2	Mean±SD visit-3	P-Value V1-V2	P-Value V1-V3	Average reduction % V1-V2	Average reduction % V1-V3
M+GL+V n=123	8.38±1.23	7.88±1.11	7.62±1.01	**<0.0017	****<0.0001	5.9%	9%
M+GP+V n= 228	9.12±0.82	8.58±0.73	8.16±0.72	****<0.0001	****<0.0001	5.9%	10.5%
M+GP+VG n=157	8.98±0.88	8.57±0.82	8.17±0.75	****<0.0001	****<0.0001	4.5%	9%
M+V+D n=210	9.33±0.98	7.98±0.80	7.13±0.60	****<0.0001	****<0.0001	14.4%	23.5%
M+S+D n= 95	9.35±0.67	7.77±0.62	6.78±0.47	****<0.0001	****<0.0001	16.8%	27.4%

Mean±SD: Represents the Average±Standard Deviation of HbA_{1C} levels measured at each visit. Visit-1, Visit-2, Visit-3: Measurements taken at baseline, 3 mo, and 6 mo post-treatment, respectively. P-Value: Statistical significance of changes between visits, determined by one-way ANOVA. ****<0.0001 indicates very high statistical significance. Average reduction % V1-V2, V1-V3: The percentage reduction in HbA_{1C} levels from Visit-1 to Visit-2 and Visit-1 to Visit-3 indicates treatment effects over time.

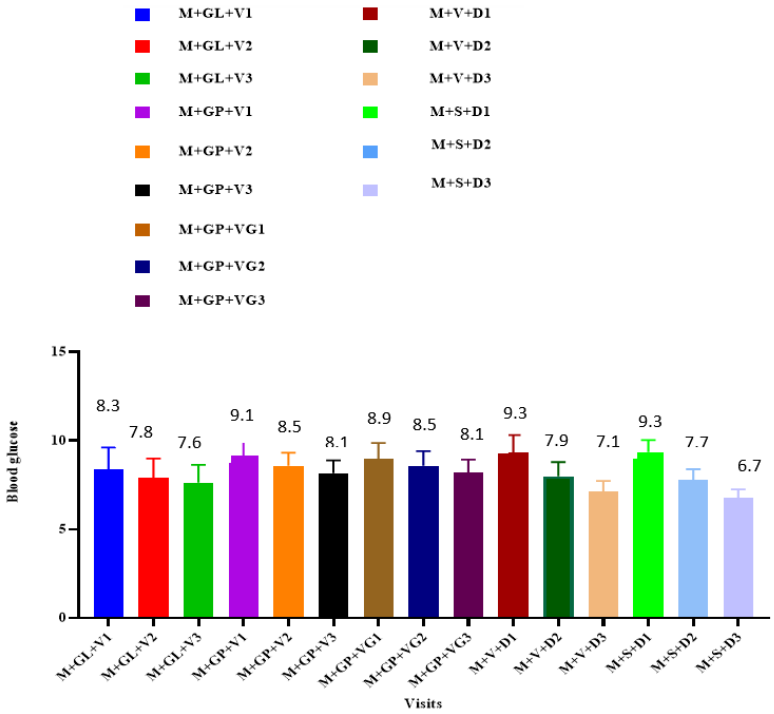


Fig. 8: Cumulative graphical representation of M+GL+V, M+GP+V, M+GP+VG, M+V+D, and M+S+D groups HbA_{1C} levels

DISCUSSION

In this study, evaluation of effectiveness of oral triple therapy regimens was done by comparing mean values, average reduction percentage and One way ANOVA followed by Tukey's multiple comparison test.

The present study includes 813 patients who were treated with different oral triple therapies (M+GL+V, M+GP+V, M+GP+VG, M+V+D and M+S+D). Out of 813 patients, 478 were found to be female and 440 were male in gender-wise distribution and most of them were found to be in the age group of 50-59, 60-69 followed by 40-49 y of age. In BMI distribution, most of them were found to be overweight (370).

In the current study Efficacy parameters of (M+GL+V, M+GP+V, M+GP+VG, M+V+D and M+S+D) groups are as follows: Total of 813 patients. Among them 123 patients received triple therapy of M+GL+V. In M+GL+V group it was observed that average FBS 154±49.54 at baseline and had 133.15± 44.97 and 124±39.12 at 3 mo and 6 mo after treatment with significant difference of P-value 0.0005 and<0.0001 respectively, average PLBS 255.15±61.07 at baseline and had 212.33±63.09 and 194.98±52.49 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001 respectively, average HbA_{1C} 8.3±1.23 at baseline and had 7.8±1.11 and 7.62±1.01 at 3 mo and 6 mo after treatment with significant difference of<0.0017 and 0.0001 respectively. Which is similar to the study done by Filozof *et al.*, 2010 revealed that the percentage of patients achieving HbA_{1C} ≤6.5% was significantly higher in patients receiving Gliclazide compared with Vildagliptin group (p=0.041) and there is significant reduction in FBS from baseline (P=0.257) [5].

The study carried out by Hyun *et al.*, 2011 demonstrated that there is significant decrease in HbA_1C (P=0.855), FBS(P=0.508) and PLBS(P=0.950) from baseline in patients who are receiving Vildagliptin-Metformin compared to Glimepiride-Metformin. Which is supported our study where 228 patients received triple therapy of M+GP+V. In M+GP+V group it was observed that average FBS 176.56±53.31 at baseline and had 144.51±33.67 and 119.329±21.638 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001 respectively, average PLBS 277.74±62.83 at baseline and had 223.61±45.78 and 186±26.88 at 3 mo and 6 mo treatment with significant difference of p-value<0.0001 and<0.0001 respectively, average HbA_{1C} at baseline 9.12±0.8 and had 8.5±0.7 and 8.1±0.7 at 3 mo and 6 mo after treatment with significant difference of<0.0001 and<0.0001 respectively [6].

157 patients received triple therapy of M+GP+VG. In M+GP+VG group it was observed that average FBS 179.56±6 at baseline and had 147.439±41.61and 123.01±28.16 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001, respectively, average PLBS 274.31±64.81 at baseline and had

220.43±47.71 and 187.36±29.41at 3 mo and 6 mo after treatment with significant difference of p-value<0.0001 and<0.0001 respectively, average HbA_{1C} at baseline 8.98±0.88 and had 8.57±0.82 and 8.17±0.75 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001 respectively. Whereas Kala *et al.,* 2017 study disclosed that Metformin with Glimepiride, Metformin with Sitagliptin and Metformin with Voglibose three groups, had equal efficacy in controlling the FBS, PLBS, and HbA_{1C} level. Only a few cases of Metformin with Glimepiride combination had mild hypoglycaemia, which subsided after food intake [7].

The study done by Mario *et al.*, 2021 disclosed that the greater proportion of reduction in HbA_{1C}(P=0.001) was observed in patients receiving Dapagliflozin compared to DPP-4 inhibitor**.** Which is similar to our study where 210 patients (n=210) received triple therapy of M+V+D. In M+V+D group it was observed that average FBS 190.78±54.61 at baseline and had143.224±36.211and 113.12±22.24 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001 respectively, average PLBS 291.54±61.28 at baseline and had 221.55±41.77 and 167.42±22.84 at 3 mo and 6 mo after treatment with significant difference of p-value<0.0001 and<0.0001 respectively, average HbA_{1C} at baseline 9.33±0.98 and had 7.98±0.80 and 7.13±0.6 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001 respectively [8].

95 patients received triple therapy of M+S+D. In M+S+D group it was observed that average FBS 190.63±47.91 at baseline and had 132.37±28.58 and 100.97±17.15 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001 respectively, average PLBS 285.9±57.34 at baseline and had193.62±29.09 and 150.64±17.42 at 3 mo and 6 mo after treatment with significant difference of p-value<0.0001 and<0.0001 respectively, average HbA_{1C} at baseline 9.35±0.67 and had7.77±0.62 and 6.78±0.47 at 3 mo and 6 mo after treatment with significant difference of P-value<0.0001 and<0.0001 respectively. Similarly, there was a study done by Jabbour *et al.*, 2014 showed that there is significant reduction in FBS (P=0.0001), PLBS(P=0.0001) and HbA_{1C} (P=0.0001) was observed in the Dapagliflozin group [9].

Present study was comparable with study done by Martin *et al.*, 2015 Triple therapy combinations included in their study are Metformin (M)+Sulfonylureas (SU) (used as reference combination); M+SU+DPP-4 inhibitor; M+SU+TZD; M+SU+GLP-1-RA; M+SU+Insulins; M+TZD+DPP-4inhibitor; M+SU+SGLT2 inhibitor. Their study showed that, in HbA_{1C} reduction, all triple therapies were statistically superior to M+SU dual therapy, except for M+TZD+DPP-4 inhibitor [10].

In the present study, safety parameters of (M+GL+V, M+GP+V, M+GP+VG, M+V+D and M+S+D) groups are as follows: In terms of safety, genital and urinary tract infections was increasingly reported in patients receiving M+S+D and M+V+D. Whereas Ghai R *et al.,* 2022 study concluded that recently approved classes, GLP-1 RA and SGLT2 inhibitors, have proved to be beneficial, they also have the potential to cause ADRs like allergic reactions and ketoacidosis, Fournier's gangrene, mycotic infections, respectively Weight gain, dizziness and incidence of Hypoglycemia were observed less in M+S+D and M+V+D group [11]. Corresponding Adverse events were reported in the study done by Jabbour *et al.*, 2014 [9].

In this study, the Nasopharyngitis and weight gain was higher in the M+GL+V and M+GP+V group compared with M+GP+VG, M+V+D and M+S+D group. Similar Adverse events were observed in the study done by Filozof *et al.*, 2010 [5] and another study done by Surendra kumar *et al.,* 2021 [12]. The study done by Filozof *et al.*, 2010 demonstrated that more number of hypoglycemic events were reported in their study, which is alike to our study, where hypoglycemia was observed more in M+GL+V and M+GP+V group [5].

CONCLUSION

From this study, it can be concluded that M+S+D and M+V+D was found to have the best efficacy in controlling the Glucose triad (FBS, PLBS and HbA_{1C}) than other triple therapy combinations (M+GL+V, M+GP+V and M+GP+VG) considered in this study.

The order of efficacy among Triple therapy combination includes:

In terms of FBS and PLBS:

M+S+D>M+V+D>M+GP+V>M+GP+VG>M+GL+V

In terms of HbA_{1C}: M+S+D>M+V+D>M+GP+V≥ M+GP+VG≥ M+GL+V

Dapagliflozin unique SGLT2 inhibition mechanism, which works independently of insulin secretion, makes it suitable for a broad range of patients.

The order of safety among Triple therapy combination includes: M+S+D>M+V+D>M+GP+VG>M+GL+V>M+GP+V

Incidence of hypoglycemia, dizziness and weight gain were observed less in M+S+D and M+V+D group whereas more number of hypoglycemic events, dizziness, weight gain and Hypotension was observed in M+GP+VG, M+GL+V and M+GP+V groups. Although Dapagliflozin use slightly raised Genito-urinary infection risk due to glucosuria, it was manageable with proper hygiene and hydration.

These findings suggest that, patients with uncontrolled T_2DM on dual therapy, switching to triple therapy regimens like M+S+D and M+V+D may improve outcomes and reduce adverse effects. These combinations showed effective glycaemic control with minimal side effects, supporting individualized, intensive treatment strategies for this patient group.

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LIMITATIONS

The study sample was limited to 813 participants, which may not fully represent the broader T_2DM population, especially across different demographics and geographical regions. The study was conducted over six months, which may not be sufficient to observe the long-term efficacy and safety of these triple therapies. Although adverse effects were recorded, the study may not have captured all potential adverse events, especially those with a low incidence rate or those that might emerge with prolonged treatment. Uncontrolled confounding factors, such as variations in patient's lifestyle, diet, or adherence to medication, may have influenced the outcomes and could not be entirely accounted for.

AUTHORS CONTRIBUTIONS

Dr. A. Makarandh, Dr. B. S. Sharvanabhava, and Dr. E. Venkateshwarlu contributed to the conception and design of the study, as well as data collection, analysis, and interpretation of results. They all participated in drafting the manuscript, critically revising it for significant intellectual content, and approving the final version for publication.

CONFLICT OF INTERESTS

The author declares no Conflict of Interest

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