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TO STUDY THE SAFETY AND EFFICACY OF SGLT2 INHIBITORS AND OTHER ORAL HYPOGLYCAEMIC AGENTS WITH INSULIN IN UNCONTROLLED TYPE 2 DM

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ABSTRACT

Diabetic mellitus is a major health care problem of India. Evidence shows that prevalence of diabetes is increasing in both urban and rural areas. Patients with diabetes have twice the risk for death than those without diabetes. With increase in prevalence of uncontrolled type 2 diabetics, newer class of ant diabetic agents such as Sodium Glucose Co transporter 2 (SGLT-2) inhibitors were introduced which has more benefits when used in combination with insulin in uncontrolled type 2 diabetic patients. **Aim:** To study the safety and efficacy of SGLT 2 inhibitors and other oral hypoglycaemic agents with insulin in uncontrolled type2 DM. **Methodology**: The study is a prospective observational study. The study population include the inpatients and Outpatients in the Department of General Medicine and Department of Endocrinology in a Teritiary Care Hospital. The total sample size recruited was 120 and divided into two different treatment groups so that each group consist of 60 patients. The study has obtained ethical clearance from institutional ethical committee. **Result**: Patients reported significantly greater reduction in HbA1c (0.0012) and FBC (0.0056) values in SGLT2 add on therapy versus other oral hypoglycaemic agents. Moreover important in the secondary outcome was also directionally and statically significantly greater in the group 1 versus group 2 as assessed under the study protocol; weight (0.0052) and BMI (0.0108). In blood pressure the systolic blood pressure (0.0789) and diastolic blood pressure (0.351) was

statistically not significant. **Conclusion**: The SGLT -2 Inhibitors are safe and effective in the treatment of Uncontrolled Type 2 DM. It has a better glycemic control and has additional benefits like weight, BMI and BP reduction. These ensure the benefit of SGLT – 2 Inhibitors with insulin as compared to other Oral Hypoglycaemic agents with insulin in uncontrolled type2 DM.

KEYWORDS: SGLT2, DM, Insulin.

INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Type 2 diabetes results from the body's ineffective use of insulin. Type 2 diabetes comprises the majority of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity.

According to the International Diabetes Federation, the global prevalence of diabetes was 8.3% in 2013, which will increase to 10.1% by 2035, and this is equivalent to approximately 3 new cases every 10 seconds.[1]

According to the World Health Organization, the prevalence of type 2 diabetes mellitus (T2DM) has almost quadrupled from the year 1980 to 2014 and was accountable for over 1.5 million deaths worldwide in the year 2012.[2]

To reduce the risk of complications in diabetes mellitus patients, it is essential to control fasting and postprandial blood glucose level and maintaining the glycemic level to the normal range as possible. Adults with diabetes have a two to three fold increased risk of heart attacks and stroke.[3] Combined with reduced blood flow, neuropathy in the leg increases the chance of foot ulcers, infection and eventual need for limb amputation. Diabetic retinopathy is an important cause of blindness and occurs as a result of long term accumulated damage to the small blood vessels in the retina.2.6% of global blindness can be attributed to diabetes.[4] Diabetes is among the leading causes of Kidney Failure.[5]

A lifestyle modification to lose weight is recommended for diabetic patients to improve glycemic control and diminish-associated risk factors of micro vascular and macro vascular complications.[6] Even modest weight loss can appreciably lessen glucose levels and decrease cardio metabolic risk factors.

In contrast to type 1 diabetes, which is treated only by insulin, different mechanisms of drugs were developed for type 2 diabetes including sulfonylurea's (SU), meglinides (MG), biguanides (BG), α-glycosidase inhibitors (AGI), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP4-I) and glucagon-like peptide-1 (GLP-1) agonists. With increase in prevalence of uncontrolled type 2 diabetics, newer class of ant diabetic agents such as Sodium Glucose Co transporter 2 (SGLT-2) inhibitors were introduced which has more benefits when used in combination with insulin in uncontrolled type 2 diabetic patients.

Among all the available OADs, SGLT2 inhibitors are the only ones which target the impaired glucose re absorption in kidney.[7] Glucose re absorption by the kidneys is mediated by specific glucose transport proteins, in particular, SGLT2. In individuals with T2DM, the capacity to reabsorb glucose and the plasma glucose concentration at which renal excretion of glucose occurs (i.e., the threshold) are elevated possibly due to up regulation of the expression of SGLT2 in the proximal tubule. Therefore, inhibition of glucose re absorption and augmentation of renal excretion of glucose are the methods by which this physiological disorder can possibly be corrected. SGLT2 inhibitors are a novel class of drugs which promote renal excretion of glucose and thereby decrease elevated blood glucose levels in patients with T2DM.[7]

The pleiotropic effects of SGLT-2 inhibitors –weight loss, BP reduction and inhibition of glucose re absorption by the kidneys make them especially attractive for use in persons with uncontrolled Type 2 Diabetes Mellitus. This class of drugs can be used in combination with insulin and its insulin sparing effect allows for more effective, well tolerated glycemic control without weight gain.

The SGLT-2 inhibitors represent a novel class of drugs which will certainly help a large number of people with diabetes to achieve target control in a safe and well- tolerated manner. Their unique mechanism of action coupled with pleiotropic benefits on weight and blood pressure should make them attractive choices for persons not controlled on other medications.

SGLT2 inhibitors, namely, canagliflozin, dapagliflozin, and empagliflozin, have been approved by the US Food and Drug Administration (FDA) for monotherapy and combination therapy in patients with T2DM.[8] The Research Society for the Study of Diabetes in India (RSSDI) has also recommended the use of SGLT2 inhibitors in the patients with T2DM.[9]

This study explores the advantage of comparing the outcomes of SGLT-2 inhibitors along with insulin and other OHAs with insulin in treatment of uncontrolled Type 2 diabetes mellitus. The study further explores the effectiveness and safety of SGLT2 inhibitors when used along with insulin in patients with T2DM. It has been suggested that the increased cost is due to the increased number of medications, increased incidence of complications such as cardiovascular risk, increased hypoglycaemic episodes and uncontrolled Hyperglycaemia.

METHODOLOGY

The study is a prospective observational study. The study population include the inpatients and Outpatients in the Department of General Medicine and Department of Endocrinology in a Teritiary Care Hospital. The total sample size recruited was 120 and divided into two different treatment groups so that each group consist of 60 patients. Group 1 consist of Patients receiving Oral Hypoglycaemic agents including SGLT2 Inhibitors along with Insulin. Group 2 consist of Patients receiving Oral Hypoglycaemic agents excluding SGLT2 Inhibitors with Insulin. Observe and collect data from patients in a well designed Data Collection Form (HbA1c, Blood Sugar, Weight, Blood Pressure, and Incidence of Hypoglycaemia). Regular follow up of patients in every 4 weeks for 6 month.

GROUP 1: Sitagliptin-Metformin (50/500mg)+ Inj. Human Mixtard (mean dose is 24.1U)+ Empagliflozin(25mg)/Dapagliflozin(10mg)/Canagliflozin (100 mg)

GROUP 2: Sitagliptin-Metformin (50/500mg) + Inj. Human Mixtard (mean dose is 28.6U)

The study has obtained ethical clearance from the institutional ethical committee. Reference no: Ec/PharmD /2018-3

Study Period: March 2018-August 2018

Inclusion Criteria

- Age above 18 years
- Patient with uncontrolled Diabetes Mellitus (ie;HbA1c >7)
- Patient on treatment with Oral Hypoglycaemic Agents with insulin both inpatients and outpatients.

Exclusion Criteria

- Patients with type1 diabetes mellitus

- Patients on irregular follow up
- Non consenting patients.
- Patients with serious co morbidities such as Renal failure patients, Chronic Liver Diseases, Cancer Treatment,
- Poisoning
- Gestational diabetes mellitus.

RESULTS AND DISCUSSION

120 patients were recruited based on inclusion and exclusion criteria. Out 120 Patients 20 patients were dropped out during the study period. 50 patients come under group 1 and remaining 50 comes under group 2. Demographic and clinical details of patients were recorded. HbA1c, FBS, weight, BMI and blood pressure (systolic and diastolic) were documented before and after add on therapy (In group 1 SGLT2 Inhibitor is the add-on therapy whereas in group 2 insulin is the add-on therapy). Incidence of Hypoglycaemia was recorded during follow up appointments in the hospital.

Table 1: Gender wise distribution data.

SL NO	GENDER	GROUP 1(n=50)		GROUP 2(n=50)	
		Number	Percentage	Number	Percentage
1	Male	29	58%	34	68%
2	Female	21	42%	16	32%

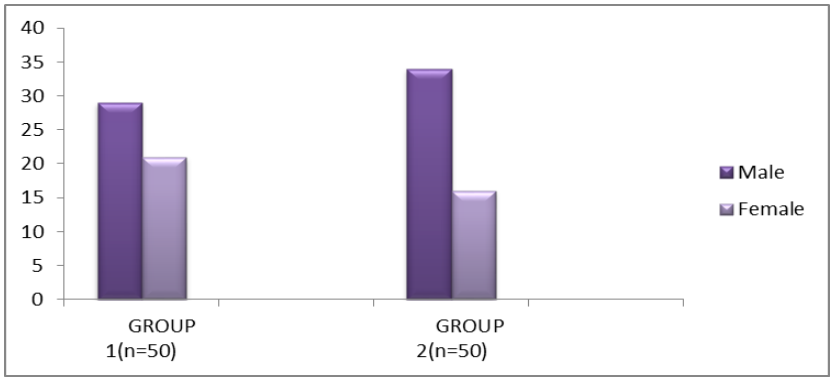

Fig. 1: Gender Wise Distribution Data.

Table 2: Age Wise Distribution Data.

Sl no	Age	Group 1 (n=50)		Group 2 (n=50)	
		Number	Percentage	Number	Percentage
1	<40 years	6	12%	5	10%
2	40 -49 years	13	26%	14	28%
3	50-59 years	15	30%	13	26%
4	>60 years	16	32%	18	36%

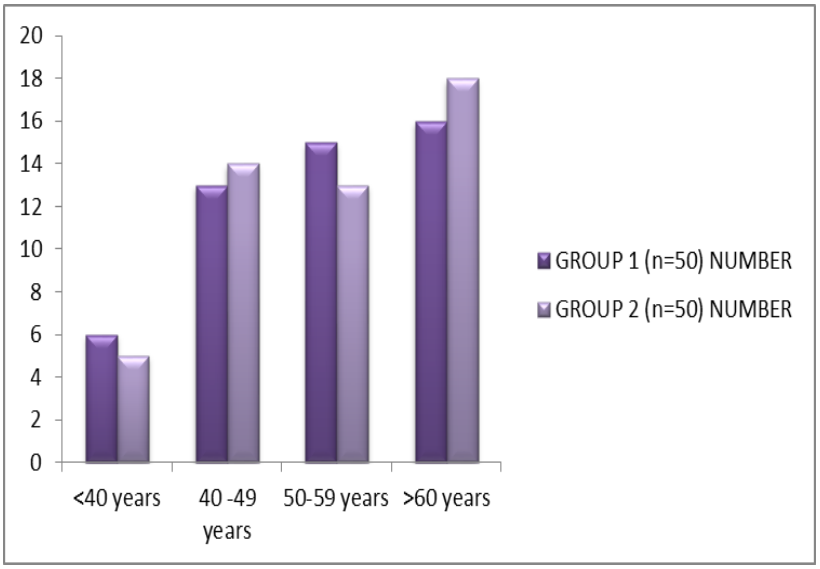

Fig 2: Age Wise Distribution Data.

Table 3: Blood pressure Status.

Sl no	Blood pressure status	Group 1 (n =50)		Group 2 (n=50)	
		Number	Percentage	Number	Percentage
1	Systemic Hypertension	8	16%	7	14%
2	Non Systemic Hypertension	42	84%	43	86%

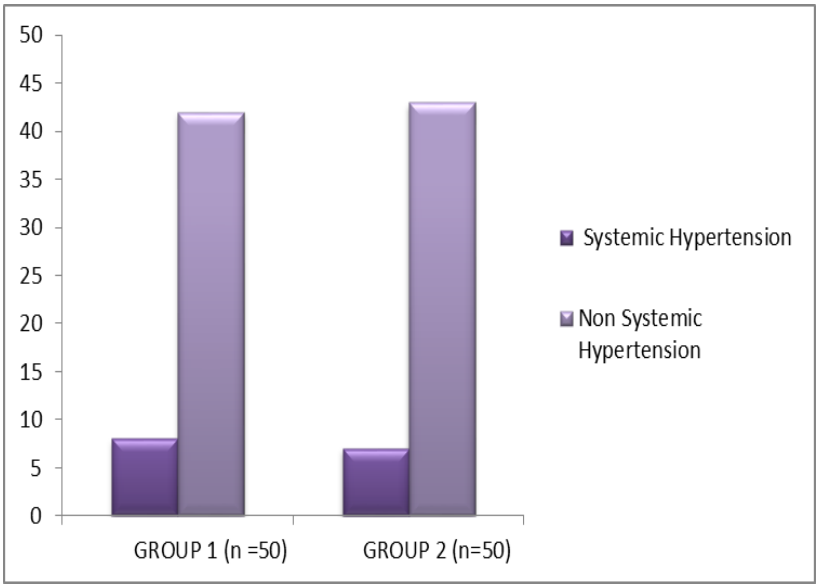

Fig 3: Blood Pressure Status.

Table 4: BMI Distribution Data.

Sl no	Bmi (kg/m2)	Group 1 (n =50)		Group 2 (n=50)	
		Number	Percentage	Number	Percentage
1	Normal (18.5 -24.9)	5	10%	6	12%
2	Overweight (25-29.9)	34	68%	31	62%
3	Obese (≥30)	11	22%	13	26%

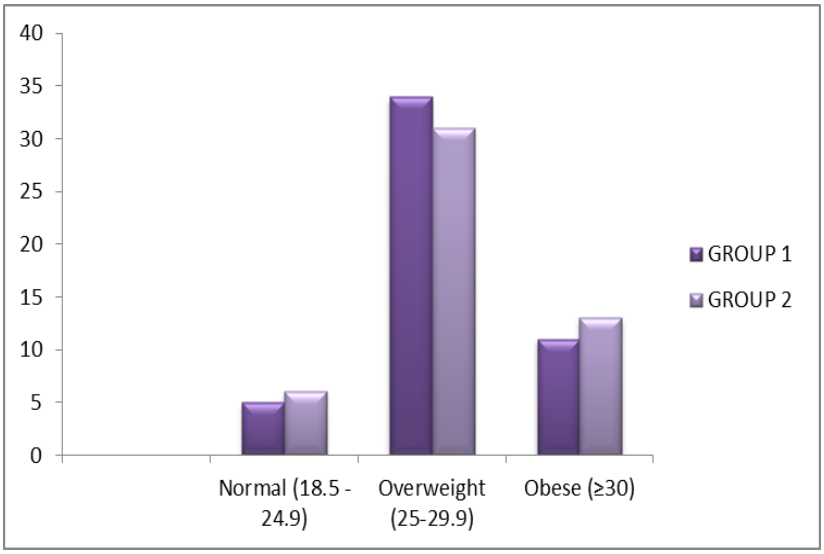

Fig 4: BMI Distribution Data.

EFFICACY PARAMETERS

Patients Diabetic Profile

Table 5: Data distribution of HbA1c.

SL NO	Time Period	HbA1c (Mean± SD)	
		GROUP 1 (n=50)	GROUP 2 (n=50)
1	Baseline	10.45±1.32	10.21±1.48
2	1st Follow up	10.12±1.21	10.18±1.38
3	2nd Follow up	9.98±1.11	9.99±1.22
4	3rd Follow up	9.37±0.98	9.79±1.09
5	4th Follow up	8.75±0.87	9.49±0.97
6	5th Follow up	7.97±0.74	8.81±0.83

Both Groups of patients had shown improvement in HbA1c after 6 months of add on therapy. The reduction of HbA1c is greater in group 1 than the group 2.

Table 6: Data Distribution of Fbs And Rbs.

Sl no	Time period	Fbs(mean±sd)		Rbs(mean ±sd)	
		Group 1(n=50)	Group 2(n=50)	Group 1(n=50)	Group 2 (n=50)
1	Baseline	212.6±62.63	182.3±79.65	382.6±62.65	328.7±80.29
2	1st Follow up	199.1±56.24	171.2±69.10	362.2±61.82	324.8±73.82
3	2nd Follow up	175.3±48.72	169.1± 62.23	353.3±59.76	319.4±69.67
4	3rd Follow up	159.2±40.68	166.4±59.91	331.5±48.44	316.3±64.32
5	4th Follow up	146.5±38.80	159.9±56.45	302.7±42.68	312.4±61.55
6	5th Follow up	138.6±33.02	154±55.81	298.3±38.06	307.8±52.43

Both groups of patients had shown improvement in FBC and RBC after 6 months off add on therapy.

Table 7: Weight and BMI.

Sl no	Time period	Weight (mean±sd)		Bmi (mean±sd)	
		GROUP 1 (n=50)	GROUP 2 (n=50)	GROUP 1 (n=50)	GROUP 2 (n=50)
1	Baseline	75.12±19.54	63.41±11.17	29.26±6.78	24.32±5.78
2	1 st Follow up	73.64±19.01	65.89±11.01	27.92±6.21	24.98±6.01
3	2nd Follow up	71.32±18.67	66.58±10.88	27.67±6.02	25.89±5.89
4	3 rd Follow up	70.99±18.21	67.01±10.03	26.76±5.77	25.45±6.12
5	4th Follow up	68.76±17.99	68.97±9.89	26.56±5.67	26.22±6.32
6	5th Follow up	67.48±17.34	69.23±9.41	25.13±5.03	26.76±7.02

Group 1 had shown reduction in weight and group 2 had shown increase in weight after 6 months of add on therapy.

BLOOD PRESSURE STATUS

Table 8: Blood Pressure of Hypertensive Patients on Anti Hypertensive.

Sl no	Time Period	Systolic blood pressure (mean±sd)		Diastolic blood pressure (mean±sd)	
		Group 1 (n=8)	Group 2 (n=7)	Group 1 (n=8)	Group 2 (n=7)
1	Baseline	151.2±3.19	149.1±4.23	99.6±4.01	97.3± 4.78
2	1st Follow up	148.1±3.08	148.9±4.19	99.1±3.98	97.6±4.02
3	2nd Follow up	144.9±3.87	146.5±3.77	98.5±3.87	96.5±3.89
4	3rd Follow up	141.5±2.65	142.9±3.89	98.1±3.54	96.4±3.78
5	4th Follow up	135.8±3.23	138.3±2.57	97.3±3.12	97.6±4.03
6	5th Follow up	132.2±2.48	136.7±2.54	95.4±3.04	96.2±3.67

Table 9: Blood Pressure on Non Hypertensive Patients.

Sl no	Time Period	Systolic Blood Pressure (mean±sd)		Diastolic Blood Pressure (mean±sd)	
		GROUP 1 (n=42)	GROUP 2 (n=43)	GROUP 1 (n=42)	GROUP 2 (n=43)
1	Baseline	130.4± 10.21	124.3±12.88	92.7±8.77	86.3±9.34
2	1st Follow up	129.3±10.01	124.6±12.04	91.8±8.75	87.2±8.12
3	2nd Follow up	127.9±9.85	123.2 ± 11.87	90.2±7.53	85.9±8.23
4	3rd Follow up	125.7± 8.56	122.8 ± 12.65	89.8±6.89	85.3± 7.87
5	4th Follow up	123.2±7.07	122.6 ±10.45	88.2±7.67	84.4±7.36
6	5th Follow up	120.3±7.65	123.4±9.34	86.9±6.54	85.2±6.43

Both groups of patients had shown reduction of diastolic blood pressure and systolic blood pressure in hypertensive patient and non hypertensive patients.

PAIRED t TEST GROUP 1

Table 10: Paired t test of HBA1c and FBS.

Sl no	Parameter	Mean	Mean Difference	N	Standard Deviation	Standard Error Mean
1	HbA1c Baseline	10.45	2.48	50	1.32	0.1866
	HbA1c After 6 Months	7.97		50	0.74	0.1046
2	FBS Baseline	212.6	74	50	62.63	8.857
	FBS After 6 Months	138.6		50	33.02	4.669

Table 11: Paired Differences of HbA1c AND FBS.

Sl No	Parameter	Mean	Standard Deviation	Standard Error Mean	95% Confidence Intervel Of The Difference		T	Df	Sig.(2 Tailed)
					LOWER	UPPER			
1	Hba1c Baseline	2.48	1.421	0.192	1.934	2.733	11.7	49	<0.0001
	Hba1c After 6 Months								
2	FBS Baseline	74	63.674	8.783	64.01	101.32	9.23	49	<0.0001
	FBS After 6 months								

HbA1c and FBS shows significant reduction after 6 months of add on therapy. The p value is less than 0.0001 for both the test (HbA1c and FBS), it is statistically significant.

Table 12: Paired t test of Weight and BMI.

Sl no	Parameter	Mean	Mean difference	N	Standard deviation	Standard error mean
1	Weight Baseline	75.12	7.64	50	19.54	2.76
2	Weight After 6 Months	67.48		50	17.34	2.45
3	Bmi Baseline	29.26	4.13	50	6.78	0.95
4	Bmi After 6 Months	25.13		50	5.03	0.71

Table13: Paired Differences of Weight and BMI.

Sl no	Parameter	Mean	Standard Deviation	Standard Error Mean	95% confidence interval of the difference		t	Df	Sig.(2 tailed)
					Lower	Upper			
1	Weight Baseline	7.64	6.231	0.863	3.61	7.223	6.058	49	<0.0001
	Weight After 6 months								
2	BMI Baseline	4.13	3.011	0.332	1.4	2.699	6.024	49	<0.0001
	BMI After 6 months								

Weight and BMI shows significant reduction after 6 months of add on therapy. The p value is less than 0.0001 for both the test, it is statistically significant.

Table 14: Blood Pressure of Hypertensive Patients on Anti Hypertensive.

Sl no	Parameter	Mean	Mean difference	n	Standard deviation	Standard error mean
1	Systolic BP Baseline	151.2	19	8	3.19	1.13
2	Systolic BP After 6 months	132.2		8	2.48	0.87
3	Diastolic BP Baseline	99.6	4.2	8	4	1.41
4	Diastolic BP After 6 months	95.4		8	3	1.06

Table 15: Paired Differences.

Sl no	Parameter	Mean	Standard Deviation	Standard Error Mean	95% Confidence Interval		T	Df	Sig.(2 Tailed)
					Lower	Upper			
1	Systolic BP Baseline	19	2.98	1.05	10.54	19.54	6.87	7	<0.0001
	Systolic BP After 6 months								
2	Diastolic BP Baseline	4.2	1.75	0.61	1.76	10.45	2.65	7	0.0074
	Diastolic BP After 6 months								

SBP and DBP in hypertensive patients on Anti hypertensive shows significant reduction after 6 months of add on therapy. The p value for SBP and DBP are <0.0001 and 0.0074 hence it is statistically significant.

PAIRED t TEST -GROUP 2

Table 16: Paired t test of HbA1c and FBS.

Sl no	Parameter	Mean	Mean Difference	N	Standard Deviation	Standard Error Mean
1	HbA1c Baseline	10.21	1.4	50	1.48	0.209
	HbA1c After 6 Months	8.81		50	0.83	0.117
2	FBS Baseline	182.3	28.3	50	79.65	11.264
	FBS After 6 Months	154		50	55.81	7.892

Table 17: Paired differences of HbA1c and FBS.

Sl no	Parameter	Mean	Standard Deviation	Standard Error Mean	95% Confidence Intervel of the Difference		T	Df	Sig.(2 Tailed)
					Lower	Upper			
1	HbA1C Baseline	1.4	2.19	0.309	0.434	1.733	3.341	49	<0.0018
	HbA1C After 6 months								
2	FBS Baseline	28.3	94.53	13.368	13.19	67.32	2.939	49	<0.0044
	FBS After 6 months								

HbA1c and FBS shows significant reduction after 6 months of add on therapy. The p value for both HbA1c and FBS are 0.0018 and 0.0044 respectively, it is statistically significant.

Table 18: Paired t test of Weight and BMI.

Sl no	Parameter	Mean	Mean Difference	N	Standard Deviation	Standard Error Mean
1	Weight Baseline	63.41	-5.82	50	11.17	1.579
2	Weight After 6 Months	69.23		50	9.41	1.330
3	BMI Baseline	24.32	-2.44	50	5.78	0.817
4	BMI After 6 Months	26.76		50	7.02	0.992

Table 19: Paired Differences.

Sl no	Parameter	Mean	Standard Deviation	Standard Error Mean	95% Confidence Interval of The Difference		t	Df	Sig.(2 Tailed)
					Lower	Upper			
1	Weight Baseline Weight After 6 months	-5.82	7.731	1.093	-6.403	-1.991	-3.836	49	<0.0006
2	BMI Base Baseline BMI After 6 months	-2.44	3.011	0.425	-2.541	-0.861	-3.852	49	<0.0004

Weight and BMI shows significant increase after 6 months of add on therapy. The p value for both weight and BMI are 0.0006 and 0.0003, it is statistically significant.

Table 20: Hypertensive Patients on Anti Hypertensives.

Sl no	Parameter	Mean	Mean Difference	N	Standard Deviation	Standard Error Mean
1	Systolic BP Baseline	149	12.3	8	4.23	1.5
2	Systolic BP After 6 months	136.7		8	2.54	0.90
3	Diastolic BP Baseline	97.3	1.1	8	4.78	1.69
4	Diastolic BP After 6 months	96.2		8	3.67	1.301

Table 21: Paired Differences.

Sl no	Parameter	Mean	Standard Deviation	Standard Error Mean	95% Confidence Interval		T	Df	Sig. (2 Tailed)
					Lower	Upper			
1	Systolic BP Baseline Systolic BP After 6 months	12.3	7.38	2.617	2.796	7.898	2.87	6	0.0109
2	Diastolic BP Baseline Diastolic BP After 6 months	1.1	4.75	1.684	-0.134	5.679	2.005	6	0.0749

SBP in Hypertensive patients on Anti Hypertensive shows significant decrease whereas DBP results in non significant reduction after 6 months of add on therapy. The p value for SBP is 0.0109, it is statistically significant. For DBP, the p value is 0.0749 and not significant statistically.

UNPAIRED t TEST

Table 22: Comparison of Group 1 And Group 2.

Sl no	Parameter	Mean Difference	P value
1	HbA1c	1.193±0.357	0.0012
2	FBS	26.17±9.341	0.0056
3	Weight	8.113±2.799	0.0052
4	BMI	2.78±1.068	0.0108
Blood Pressure In Hypertensive Patients			
1	Systolic BP	6.359±3.588	0.0789
2	Diastolic BP	1.730±1.788	0.351

The 2 groups were compared using unpaired t test, HbA1c, FBS, Weight and BMI shows significant differences whereas BP did not result any significant differences.

DISCUSSION

Total 100 patients was enrolled and divided into two groups. Patient enrolled in both groups were comparable with each others to age, gender, BMI, blood pressure, HbA1c and FBC for 6 months.

This present prospective observational study evaluated the safety and efficacy of SGLT2 inhibitor and other oral hypoglycaemic agent with insulin in uncontrolled type 2 DM. Patients reported significantly greater reduction in HbA1c(0.0012) and FBC(0.0056) values in SGLT2 add on therapy versus other oral hypoglycaemic agents.

Moreover important in the secondary outcome was also directionally and statically significantly greater in the group 1 versus group 2 as assessed under the study protocol; weight (0.0052) and BMI (0.0108). In blood pressure the systolic blood pressure (0.0789) and diastolic blood pressure (0.351) was statistically not significant.

Analysis of all the primary and secondary measures demonstrated that treatment with these SGTL2 inhibitors reduced HbA1c and FBC level in type 2 DM at 6 months in the study population.

Four other published trials using this SGLT 2 Inhibitors in type 2 DM. SGLT 2 Inhibitors have favourable effect on combating hyperglycaemia.[10] SGLT2 Inhibitors compared with DDP4 inhibitors[11] and sulfonylurea.[12] SGLT2 inhibitors have improved the HbA1c and FBC and they have additional benefits beyond glycemic control such as reducing weight and lowering blood pressure.[13]

CONCLUSION

The SGLT -2 Inhibitors are safe and effective in the treatment of Uncontrolled Type 2 DM. It has a better glycemic control and has additional benefits like weight, BMI and BP reduction. These ensures the benefit of SGLT – 2 Inhibitors with insulin as compared to other Oral Hypoglycaemic agents with insulin in uncontrolled type2 DM.

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