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SAFETY OF INSULIN ADD ON THERAPY AND ORAL HYPOGLYCEMIC AGENTS (OHGAs) POLYPHARMACY IN TYPE - II DIABETES PATIENTS - A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objectives: A clinical observational study conducted to compare the safety of Insulin add-on therapy and Oral Hypoglycemic Agents (OHGAs) polypharmacy and to promote safe use of insulin and OHGAs in Type II Diabetes patients, through patient counseling by Clinical pharmacist at Government General Hospital, Guntur. **Methods:** A Prospective Observational study was conducted on Type II Diabetes mellitus patients in General Medicine department in a tertiary care hospital, during the period of March to August of 2014. The work was carried out by using patient data collection forms and Diabetes questionnaire. **Results:** Among 193 study population with Type II Diabetes, OHGAs polypharmacy 46.25% (n=108) was found to be more than Insulin alone and Insulin add on therapy. **Conclusion:** From the study it was found that patients who are on OHGAs polypharmacy were subjected to GI disturbances and who are on Insulin therapy were subjected to hypoglycemic episodes. Considering the key role of pharmacist the safety of antidiabetic medications and adherence was improved through patient counseling.

KEYWORDS: Insulin, safety, OHGAs, type II DM.

INTRODUCTION

Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin that it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia).

The primary objective of diabetes management is to achieve satisfactory levels of glycaemic control, which reduces the risk of associated serious, long-term complications.[1, 2] Literature suggests that the majority of people with type 2 diabetes (T2D) worldwide are not achieving targeted glycemic levels.[3] The T2D is characterised by progressive loss of beta cell function requires concurrent changes in treatment to maintain adequate glycemic control, mostly require insulin therapy to achieve this.[4] Due to distinguished pharmacodynamic and pharmacokinetic profile and based on evidence of their efficacy and safety in clinical trials, now a day's insulin analogues are gaining wide acceptance and are frequently prescribed.[5] Most patients begin treatment with diet and exercise with or without treatment regimen but, unfortunately most patients are unsuccessful in controlling type 2 diabetes through lifestyle modification alone and require antidiabetic agents. In poorly controlled diabetics there is a requirement for intensified and multidrug regimens, ultimately, oral agents alone cannot be the mainstay treatment for glycaemic control in many individuals and therapy must be added by the addition of insulin. Therefore this study is conducted with the aim to compare the safety (adverse effects, contraindications and Drug-Drug interactions) of the two possible approaches i.e OHGAs polypharmacy and insulin add on therapy for managing failure of combination therapy with oral medication only.[6]

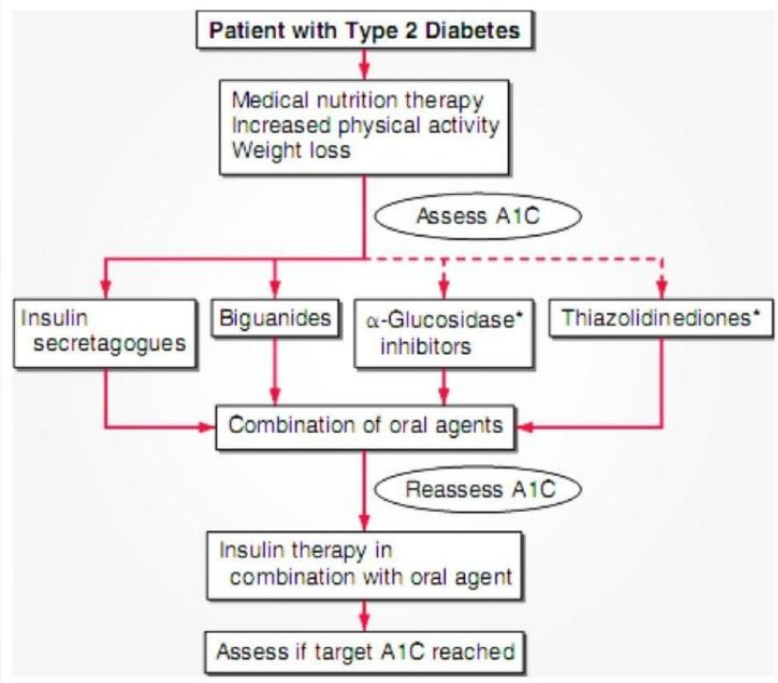


Figure 1: Standard Treatment Guidelines for Type 2 Diabetes Mellitus

Note: The broken line indicates that biguanides or insulin secretagogues, but not glucosidase inhibitors or thiazolidinediones, are preferred for initial therapy[1].

Table 1: Nutrition Therapy for Diabetes Mellitus

MEDICAL NUTRITION THERAPY	
Nutrition therapy for all patients with diabetes as part of overall treatment plan	
Prediabetes or diabetes Individualized medical nutrition therapy as needed to achieve treatment targets, preferably provided by registered dietitian.	
Individuals at high risk for developing type 2 diabetes	
Being structured program emphasizing life style changes,	• Moderate weight loss (7% body weight) • Regular physical activity (150 min/ wk) with dietary strategies
including -	including reduced calorie and fat intake.
Achieve dietary fiber intake of 14g/1000 k cal and whole grains 50% of grain intake	

Table 2: Physical Activity in Type Ii Diabetes Mellitus

PHYSICAL ACTIVITY
Adults with diabetes
Exercise programs should include • ≥ 150min/wk moderate – intensity aerobic activity (50% - 70% max heart rate), spread over • ≥ 3 days/wk with no more than 2 consecutive days with out exercise. • Resistance training ≥ 2 times/wk (in absence of contraindications)
Evaluate patients for contraindications prohibiting certain types of exercise before recommending exercise program.
Consider age and previous level of physical activity.
Children with diabetes/ prediabetes - ≥ 60 min hysical activity/day.

Table 3: Oral Hypoglycemic Agents

Medication	**Mechanism of Action**	**Side Effects**	**Contraindications**
Biguanides Metformin	Reduce gluconeogenesis, increase glucose uutilisation	Lactic acidosis, anorexia, Vit B12 deficiency, nausea, diarrhoea, GI dyscomfort	Hepatic or renal impairment, alcoholism, advanced age
Sulphonyl ureas Glibenclamide glimepride Glipizide Gliclazide	Stimulates release of endogenous insulin	Significant hypoglycaemia, nausea, GI dyscomfort	Hepatic or renal impairement
Thiazolidinediones	Increase peripheral	Increased TG,	Liver disease
Rosiglitazone Pioglitazone	insulin sensitivity, reduce gluconeogenesis	weight gain, hepatotoxicity, anemia	Congestive heart failure
Meglitinides Repaglinide	Stimulate release of endogenous insulin	Less frequent hypoglycemia	Hypersensitivity Diabetid ketoacidosis
Alpha glucosidase inhibitors Acarbose	Decrease the absorption of carbohydrates	Flatulence, abdominal cramping, diarrhoea	Hypersensitivity, DKA, IBD

Table 4: Hypoglycemia Management

At risk patients	Ask about symptomatic and asymptomatic hypoglycemia at each encounter
Preferred treatment: glucose(15-20 g) • After 15 mins of treatment, repeat if hypoglycemia continues(per SMBG) • When SMBG normal: patient should consume meal or snack to prevent recurrence	
Prescribe glucagon if significant risk of severe hypoglycemia	
Hypoglycemia unwareness or episode of severe hypoglycemia	Reevaluate treatment regimen Insulin-treated patients: raise glycemic targets for several weeks to partially reverse hypoglycemia unawareness and reduce recurrence
Low or declining cognition	Continually assess cognitive function with increased vigilance for hypoglycemia.[9]

A reasonable initial dose is 20 g of glucose. If neuroglycopenia precludes oral feedings, parenteral therapy is necessary. Intravenous glucose (25 g) should be given using a 50% solution followed by a constant infusion of 5 or 10% dextrose. If intravenous therapy is not practical, subcutaneous or intramuscular glucagon can be used, particularly in patients with type 1 diabetes mellitus. Because it acts primarily by stimulating glycogenolysis, glucagon is ineffective in glycogen-depleted individuals (e.g., those with alcohol-induced hypoglycemia). It also stimulates insulin secretion and is therefore less useful in type 2 diabetes mellitus. These treatments raise plasma glucose concentrations only transiently, and patients should be encouraged to eat as soon as practical to replete glycogen stores.[7]

AIMS AND OBJECTIVES

Aims

A clinical observational study on safety of Insulin add on therapy and OHGA polypharmacy in type 2 diabetic patients attending general medicine ward in government general hospital, Guntur from March - August 2014.

Objectives

- To compare safety of insulin addon therapy and Oral hypoglycemic agentspolypharmacy.
- To promote safe use of insulin through patient counseling by clinical pharmacist.

Plan of work

The work is planned to carry out as following:

- To include type 2 diabetes mellitus patients.
- To design a patient data collection form and diabetes questionnaire.

- To collect all the data required for the study from general medicine ward
- To analyse the data and provide the feedback of results to the physician (prescriber) and submit the safety data of insulin add on therapy and OHA's polypharmacy in type-2 DM
- To counsel the patients regarding the usage of medications.

METHODOLOGY

Study site: A Non experimental prospective observational study was conducted on type-2 diabetes mellitus patients in general medicine department, GOVERNMENT GENERAL HOSPITAL, Guntur, Andhra Pradesh.

Study period

The study is being conducted from April to September of 2014.

Inclusion criteria

• Subjects more than 18years of age with Type II diabetes.
• FBS must be > 130 mg/dl.
• Both inpatients and outpatients who consulted the general medicine department.
• The patients who are willing to participate in the study.

Exclusion criteria

• Critically ill patients who cannot participate in the study.
• Subjects with Type I DM.
• Subjects on OHGA monotherapy.
• Patients who are not willing to participate in the study.

Study design

A Non Experimental prospective observational study.

STUDY METHOD

• Study is conducted in Government General Hospital, Guntur, a1300 bedded tertiary care hospital.
• All patients with Type 2 diabetes mellitus will be included in the study.
• Most of the patients visiting the hospital are from rural areas
• Patients were screened for FBS/RBS/PPBS level and FBS must be > 130 mg/dl were considered.

• Evaluation of clinical symptoms, FBS/RBS/PPBS levels in patients on Insulin add on therapy and OHGA polypharmacy for better glycemic controland adherence, safety parameters were assessed.

• The baseline knowledge of the patients on the disease, complications, regular blood glucose monitoring, diet, life style modifications and medication adherence is assessed using a questionnaire.

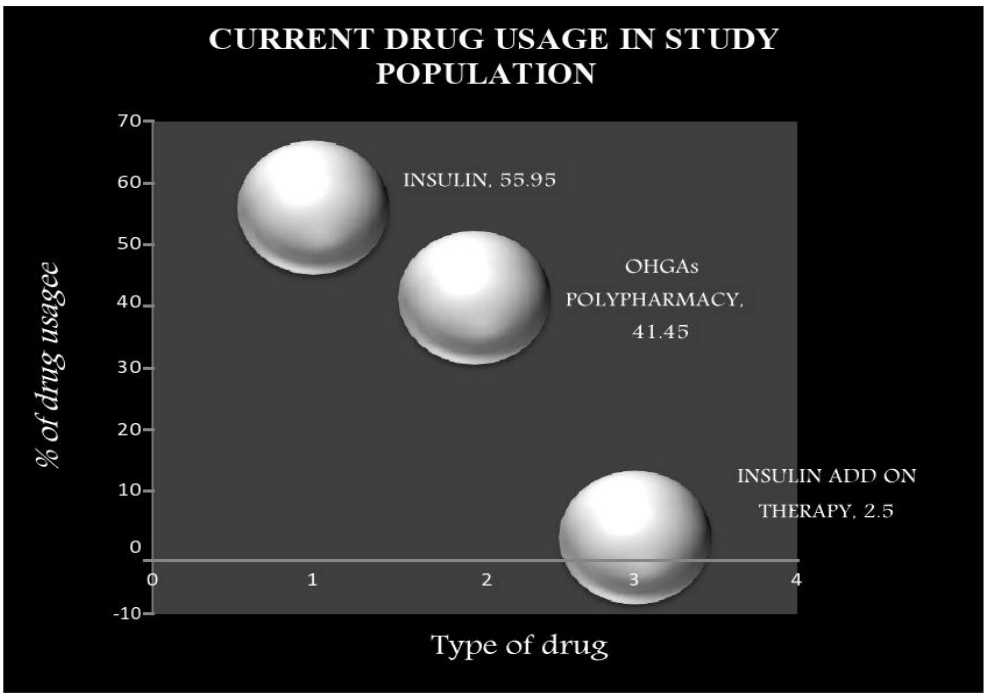
• Patients are then counselled about disesase, diet, life style modifications and medication adherence.

• Patients are reviewed periodically (i.e., every 3 months) for the improvement in their blood sugar levels and improvement in general condition.

RESULTS

Table 5: Current Drug Usage

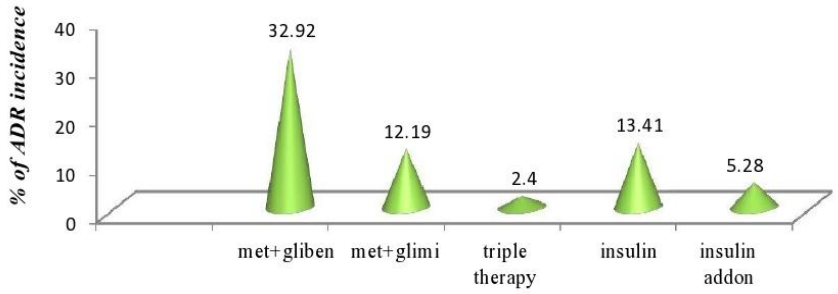
Type of drug	Drug usage in no. persons	% of drug usage
Insulin	80	55.95
OHGA's poly pharmacy	108	41.45
Insulin addon therapy	5	2.5



Graph 1: Current Drug Usage

Table 6: ADR Occurrence in Different Drug Therapies

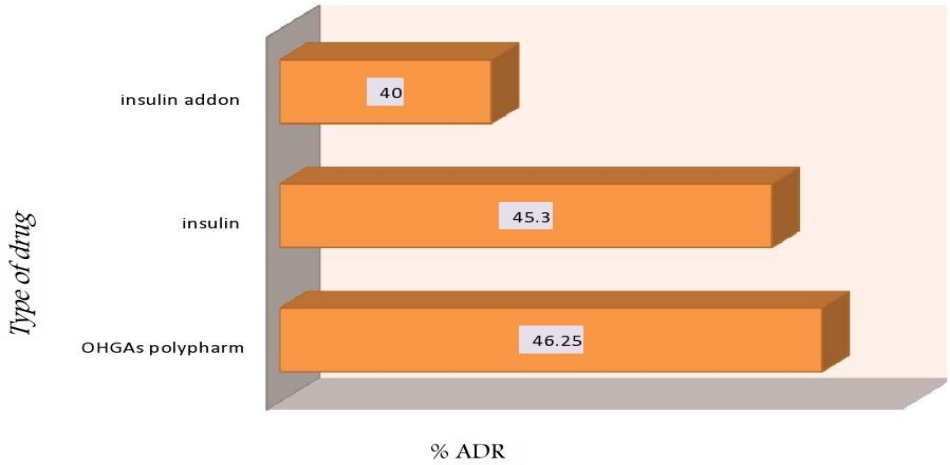
Type of drug	Overall ADR occurrence	% ADR occurrence
Metformin+glibenclamide	81	32.92
Metformin+glimipride	30	12.19
Triple therapy	6	2.4
Insulin	33	13.41
Insulin add on therapy	13	5.28



Graph 2: ADR Occurrence in Different Drug Therapies

Table 7: % of ADR in Current Treatment

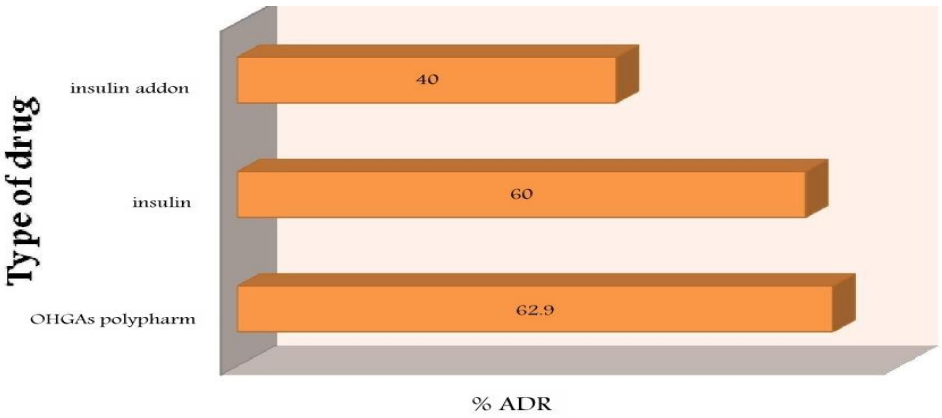
Drug	Total no. exposed	ADR occurrence	% ADR
OHGA's polypharmacy	80	37	46.25
Insulin	108	49	45.3
Insulin addon therapy	5	2	40



Graph 3: % of ADR in Current Treatment

Table 8: % of ADR in Past Treatment

Drug	Total no exposed	ADR occurance	% ADR
OHGAs polypharm	116	73	62.9
Insulin	5	3	60
Insulin addon therapy	5	2	40

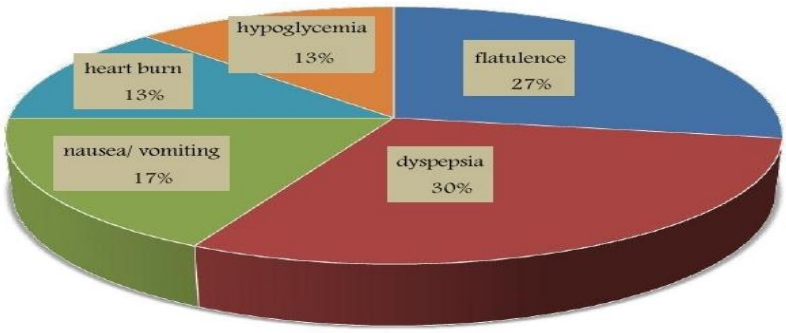


% ADRS OF OHGAS POLYPHARMACY

Graph 4: % of ADR in Past Treatment

Table 9: % ADRS of Ohgas Polypharmacy

Type of ADR	ADR occurrence	Polypharmacy
Flatulence	22	27.5
Dyspepsia	24	30
Nausea/ vomiting	14	17.5
Diarrhoea	0	0
Heart burn	10	12.5
Hypoglycemia	10	12.5

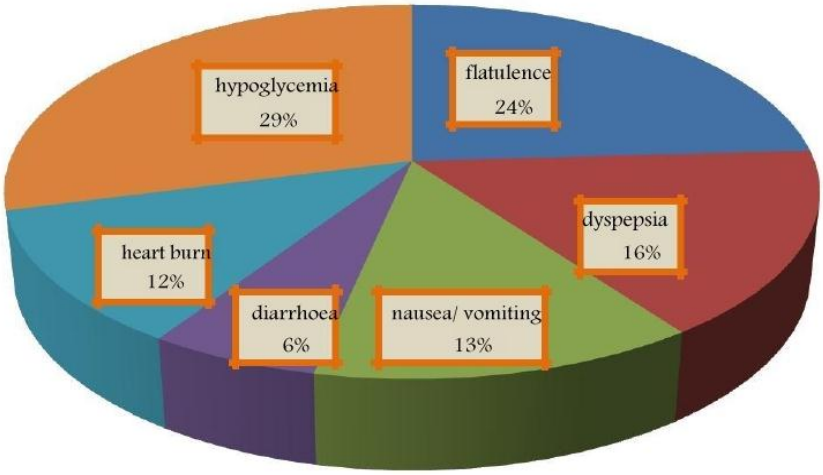


% ADRS OF INSULIN ADD ON THERAPY

Graph 5: % ADRS of Ohgas Polypharmacy

TABLE 10: % ADRS of insulin add on therapy

Type of ADR	ADR in no	% ADR occurrence
Flatulence	16	24
Dyspepsia	11	16
Nausea/ vomiting	9	13
Diarrhoea	4	6
Heart burn	8	12
Hypoglycemia	20	29

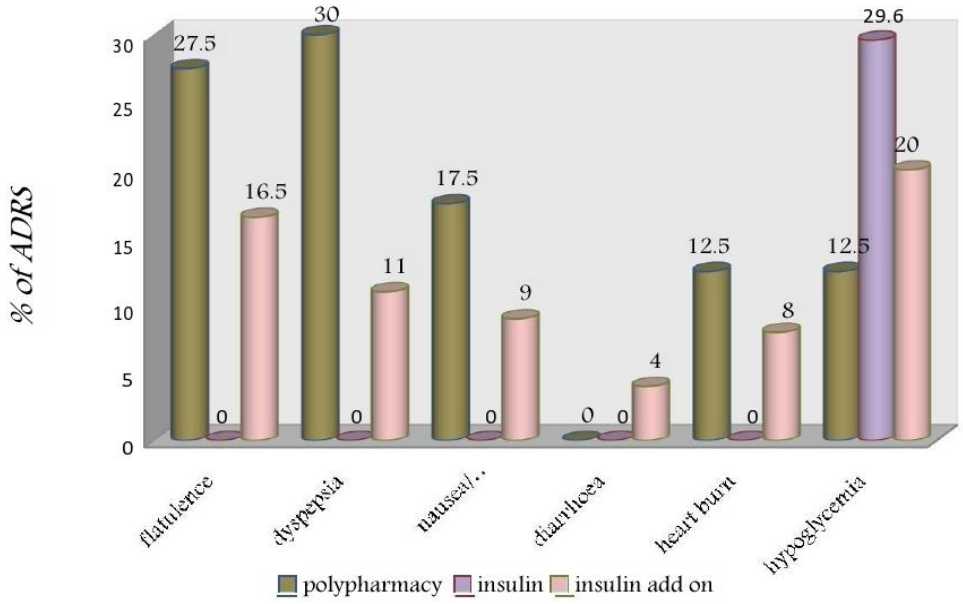


ADRS OF ANTIDIABETIC AGENTS

Graph 6: % ADRS of insulin add on therapy

Table 11: ADRS of antidiabetic agents

Type of ADR	Polypharmacy	Insulin	Insulin addon therapy
Flatulence	27.5	0	16.5
Dyspepsia	30	0	11
Nausea/ vomiting	17.5	0	9
Diarrhoea	0	0	4
Heart burn	12.5	0	8
Hypoglycemia	12.5	29.6	20

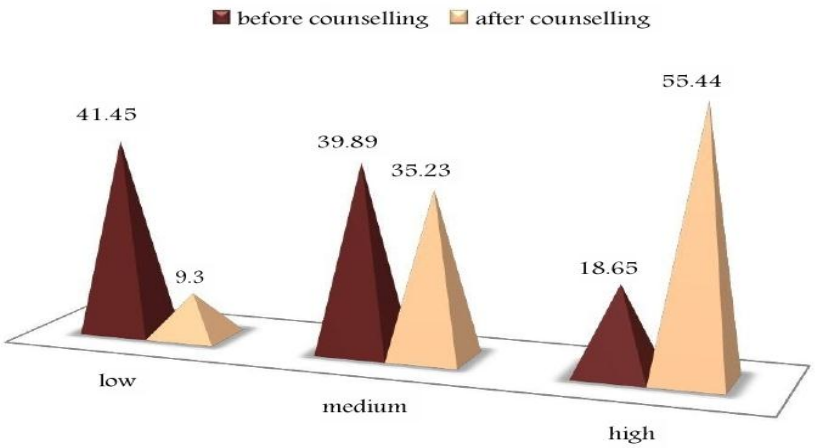


IMPACT OF COUNSELLING ON MEDICATION ADHERENCE

Graph 7: ADRS of antidiabetic agents

Table 12: Impact of counselling on medication adherence

Adherence	Before counselling		After counseling	
Low	80	41.45%	18	9.3%
Medium	77	39.89%	68	35.23%
high	36	18.65%	107	55.44%



Graph 8: Impact of counselling on medication adherence

DISCUSSION

A prospective observational study done in a tertiary care hospital during the period of March – August, 2014 in type 2 diabetic patients, on safety of Oral hypoglycaemic agents

polypharmacy (OHGAs) and insulin add on therapy to OHGAs and promotion of safe use of antidiabetic medications through patient counseling.

The OHGAs to which the patient population exposed currently are combination of metformin and glibenclamide; metformin and glimepride; metformin and glipizide; metformin, glimipride and pioglitazone; metformin, glimipride and voglibose, insulin alone and insulin add on therapy with OHGAs.

Considering the antidiabetic usage currently OHGAs polypharmacy (108 out of 193) was found to be more than insulin alone (80 out of 193) and insulin add on therapy (5 out of 193) responsible increased occurrence of ADRs like flatulence (27.5%), dyspepsia(30%), nausea/vomiting(17.5%), heart burn(12.5%), hypoglycaemia(12.5%) in OHGAs polypharmacy and flatulence (24%), dyspepsia(16%), nausea/vomiting(13%), diarrhoea(6%) heart burn(12%), hypoglycaemia(29%) in insulin add on therapy. Except hypoglycaemia the occurance of all other ADRs were comparatively less in patient population on insulin add on therapy than OHGAs polypharmacy.

CONCLUSION

Hence the safety assessment i.e. ADR occurrence, sub therapeutic and toxic responses, adherence to medication were carried out in study population who are on antidiabetic agents like OHGAs polypharmacy, insulin alone, insulin add on therapy considering FBS/ RBS , physical symptoms, questionnaire as evaluating parameters.

Considering the key role of pharmacist the safety of antidiabetic medications and adherence was improved through patient counselling on disease, proper drug usage (how to take, when to take, how much to take, how long to take, with what we have to take medication, do's and don'ts while administering antidiabetic medication, possible side effects and contraindications, advantages of taking medication), diet (daily calorie intake, diet chart, foods to be taken and to be avoided), physical activity (what to do ?, how long to do?) which reduced the ADRs, economical burden with its management and worsening condition due to withdrawl of medication and promoted the quality of life of patient.

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