

## COMPARATIVE EFFECTIVENESS OF MULTI ORAL ANTIDIABETIC DRUGS VERSUS INSULIN THERAPY FOR GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

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### ABSTRACT

**Objective:** Most antihyperglycemic drugs other than insulin reduce glycosylated hemoglobin (HbA1c) to similar levels but differ in respect to pathophysiological effects and safety. The decline in blood sugar control with oral anti-diabetic relates to many factors, as progressive loss of beta cell function, comorbidities, lifestyle factors, and glucotoxicity. The study objective was examination of safe, sustained reduction of HbA1c, by the modification of diabetes disease course, and averting complication. Insulin in real life practice with appropriate current oral drugs and supplementary insulin regimen.

**Methods:** Herein, a comparative study spanning 6 months outdoor management of Type 2 diabetes patients on triple oral anti-diabetic drug regimen (26 patients) and on premix insulin regimen (34 patients) was undertaken at a tertiary care center in Central India.

**Results:** The study reveals that addition of insulin in poorly controlled Type 2 diabetes patients on metformin and sulfonylurea treatment, achieve a higher reduction of HbA1c as well as fasting plasma glucose and postprandial glucose control than the three-drug combination therapy comprising metformin, sulfonylurea plus acarbose. However, there is only some increase in the risk of hypoglycemia.

**Conclusion:** Premix insulin can be preferred in older, long disease bearing patients where too tight glycemic control is not envisaged, and shall be balanced safe and efficacious treatment.

**Keywords:** Type 2 diabetes mellitus, Insulin therapy, Triple oral anti-diabetic therapy, Premix insulin.

### INTRODUCTION

Professional organizations endorse target glycosylated hemoglobin (HbA1c) levels for diabetes control. These provide practical safe goals for reduction of complications. As the disease advances, it becomes difficult to achieve or maintain target HbA1c levels of 6-7%. Most anti-hyperglycemic drugs other than insulin reduce HbA1c to similar levels but differ in respect to pathophysiological effects and safety [1]. The decline in blood sugar control with oral anti-diabetic relates to many factors, as progressive loss of beta cell function, comorbidities, lifestyle factors, and glucotoxicity [2]. Examination of safe, sustained reduction of HbA1c, by the modification of diabetes disease course and averting complication insulin in real life practice with current drugs has not been adequately performed. Studies on such line have hinted that patients with features of insulin resistance such as fatty liver, high serum triglyceride, and low high-density lipoprotein cholesterol would benefit more by initial treatment with metformin, pioglitazone, and glucagon-like peptide-1 receptor antagonists. The lean patients with long standing disease may more benefit by dipeptidyl peptidase 4 inhibitors and sulfonylureas with early addition of insulin. Other drugs as alpha glucosidase inhibitors and sodium-glucose co-transporter 2 inhibitors may help to lower HbA1c level with less risk of hypoglycemia and weight gain [3,4].

Insulin is the most cost-effective intervention, when combined treatment with two or more oral agents fails to achieve glycemic target [5]. Insulin therapy involves injecting self. There is also fear of weight gain and risk of hypoglycemia. These aspects undermine treatment compliance. Multiple oral drug combinations, on the other hand, increase the risk of adverse drug reactions and costs.

Current commonly initiated insulin therapy can be basal insulin analogue, usually given at bed time; or with premix insulin analogue along with breakfast and dinner [6]. Insulin yields greater reduction

of HbA1c, especially where prevailing level is above 8.5% [7-9]. This study evaluated effectiveness and safety of switching to premix insulin (30% insulin aspart +70% intermediate-acting protamine-aspart insulin) [10] therapy versus oral anti-diabetic combinations for the patient not accepting the former.

### METHODS

It was hospital based prospective observational study conducted in medicine outdoor patients at Index Medical College, Indore, from September 2015 to May 2016. Adult Type 2 diabetes patients under 65 years old age with prevailing HbA1c level between 7.5% and 10% despite oral anti-diabetic therapy and fasting blood glucose level above 139 mg/dl formed the study subjects. Exclusion criteria were creatinine levels above 1.4 mg/dl indicating renal disease or alanine aminotransferase activity 2.5 times the upper normal limit, indicating liver dysfunction. The observational study objectives and processes were explained, and written consent for participation was sought from patients.

### Drug therapy

About 26 patients received combination therapy of metformin, sulfonylurea and acarbose. 34 subjects in insulin group received twice daily premixed insulin formulation subcutaneously before breakfast and at bedtime. Fasting plasma glucose (FPG) and postprandial glucose (PPG) plasma glucose levels were guide to dose determination. HbA1c levels were determined initially and next at 3 and 6 months on therapy. The proportion of cases in the groups achieving HbA1c level under 7% were noted. Safety of therapy was assessed by observation of hypoglycemic episodes. Minor hypoglycemia were instances of blood glucose dropping below 56 mg/dl with or without symptoms and reversed by self-care. Major hypoglycemia consisted neurological symptoms and necessitating medical care.

Differences of findings between groups for quantal values was tested by Chi-square and graded values by Student's t-statistical tests.

## RESULTS

As obvious, no other characteristics except HbA1c levels exhibited any significant difference between two groups (Table 1).

The progress of change in HbA1c level in the compared groups at 3 and 6 months of therapy were as shown in Table 2.

Glycosylated Hb concentration significantly decreased in insulin treatment group ( $p=0.01$ ) but significantly increased in triple oral drug regimen group ( $p=0.05$ ). Final HbA1c levels attained in two groups were not significantly different from each other. In the insulin treatment group, 11 of 34 cases achieved below 7% and 19% of 34 below 8% HbA1c levels. In the 26 cases of oral therapy 7 achieved HbA1c under 7% and 12 achieved under 8%.

The profile of FPG and PPG were checked monthly. The change from initial to that at 6 months therapy was as shown in Table 3.

Only the decline in FPG and PPG in the insulin treatment group were statistically significant, respectively, at  $p=0.05$  and  $p=0.001$ .

**Table 1: Presents baseline patient profiles in the two treatment groups at initiation**

Parameters	Insulin group	Tripple oral drug group	p
N	34	26	0.05
Age in years	62.2±10.2	60.3±11.6	
Sex			
Males	19	11	
Females	15	15	
Duration of DM (years)	13.1±8.2	12.5±7.7	
HbA1c %	8.9±2.1	8.1±1.9	
FPG mg/dl	169.5±80.3	160.4±58.8	

HbA1c: Glycosylated hemoglobin, DM: Diabetes mellitus, FPG: Fasting plasma glucose

**Table 2: Comparative HbA1c profiles of patients in the regimens**

HbA1c testing	Insulin group	Tripple oral drug group	p
Initial	8.9±2.1	8.1±1.9	0.05
3 months	8.52±2.2	8.37±2.1	
6 months	8.31±1.9	8.75±2.4	

HbA1c: Glycosylated hemoglobin

**Table 3: Comparative Blood Glucose Profiles of patients in the regimens**

Blood glucose	Insulin group		Tripple oral drugs group	
	Initial	At 6 months	Initial	At 6 months
FPG mg/dl	169.5±80.3	138.5±72.2	160.4±58.8	171.1±65.4
PPG mg/dl	238.3±91.3	192±102.2	210.2±98.4	217.7±104.2

FPG: Fasting plasma glucose, PPG: Postprandial glucose

**Table 4: Comparative instances of Hypoglycaemia in patients in the regimens**

Hypoglycemic episodes	Insulin group	Tripple oral drug group
Minor episodes n (%)	12 (35)	7 (26.5)
Major episodes n (%)	1 (3)	1 (4)

Safety profile as observed in terms of minor and major hypoglycemic episodes is presented in Table 4.

## DISCUSSION

No single antihypertensive agent may correct varied metabolic pathophysiology in diabetes and hence therapy combining agents acting by different mechanisms is required in most cases to bring down HbA1c [11]. Precise choice of pharmacological agent remains topic of debate, partly because different classes of drugs associate varied safety concerns. Optimal regimen ought to address key perspectives of insulin resistance and beta cell failure, to achieve durable glycemic control. The benefits and harms of therapy must be appropriately balanced. HbA1c measurements assess long-term glycemic target achievement [5]. The oral drugs initially do yield glycemic control, eventually insulin is required [12]. Patients with beta cell failure on optimal oral doses of anti-diabetic drugs, present with fasting blood sugar more than 140 mg/dl, postprandial more than 180 mg/dl and HbA1c at level 2% higher than upper limit of normal. Such patients need exogenous insulin supplement [13]. When HbA1c is close to treatment goal, e.g., 8%, addition of the 3<sup>rd</sup> oral agent is considered as an option before adding insulin [14]. Further lowering of HbA1c, however, would need insulin [15]. Natural history of Type 2 diabetes is that most patients develop insulin deficiency to an extent that warrants starting prandial insulin in addition to basal insulin [16]. One may add rapid acting insulin with one of the daily meals (basal plus regimen). Alternatively, rapid insulin may be added with 2-3 daily meals (basal-bolus regimen) or switch to premix insulin [17]. Basal insulin is naturally preferred as addition to anti-hyperglycemic drugs. Adherence to therapeutic regimen is crucial concern and lesser the number of injections better is adherence [18]. Factors such as patient preference, life expectancy, disease duration, comorbid conditions, socio-economic status, and cognitive abilities of the patient would guide choice of therapy regimen.

In this study, regimen of premix insulin formulation exhibited limited ability to achieve target for HbA1c in only third of patients. Premix insulin provides for less error in dosing but has limited flexibility to adjust for diet and lifestyle. The choice of anti-diabetic therapy influences the risk of hypoglycemia also. Insulin therapy aims at simulating the natural pattern of insulin output throughout the day. Thus, it prevents preprandial glucose troughs and PPG peaks. Insulin analogues have made for potential delivery of near physiological insulin therapy [19].

Insulin 70/30 mix plus metformin regimen has been proposed to offer substantial cost reduction compared to the triple oral anti-diabetic drug regimen [20]. Other ad-on insulin regimens also serve economic objective, limited however by risk of hypoglycemic episodes [15]. Low-dose insulin glargine combined with sulfonylurea and metformin is reported to give similar reduction of HbA1c (or even higher reductions if baseline HbA1c is more than 9.5%), compared to that obtainable with ad-on maximum rosiglitazone [21].

## CONCLUSION

This study reveals that addition of insulin in poorly controlled Type 2 diabetes patients on metformin and sulfonylurea treatment, achieve higher reduction of HbA1c as well as FPG and PPG control than the three-drug combination therapy comprising metformin, sulfonylurea plus acarbose. There is only some increase in the risk of hypoglycemia, however. Premix insulin is preferable for patients not compliant to basal-bolus treatment, and in whom too strict glycemic control is not mandatory, while they have well organized daily life [22,23].

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