

A Single-Center, Observational, Retrospective Cost-Effective Analysis of Treating Inadequately Controlled Type 2 Diabetes Mellitus by Addition of DPP4 Inhibitors Versus Intensified Treatment with Conventional Drugs

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Abstract

Objective: To compare the cost effectiveness and achievement of glycemic goals in patients inadequately controlled by conventional drugs receiving either intensified treatment or DPP4 inhibitor as an add on. It shall help us to identify a preferred choice of treatment. **Materials and Methods:** As per study protocol, 52 patients with inadequately controlled type 2 diabetes mellitus (DM) were included in the study. They received either intensified treatment or add-on with DPP4 inhibitor. Glycated hemoglobin (HbA1c), fasting blood sugar (FBS), postprandial blood sugar (PPBS), adverse drug reactions, and their cost were calculated for the next 6 months of therapy. **Results:** Add on therapy with DPP4 inhibitor showed a greater achievement of glycemic goals. Target HbA1c was achieved by 58.6% ($P < 0.0001$) versus 40% ($P < 0.05$), FBS was achieved by 78.50% ($P < 0.0001$) versus 50% ($P < 0.16$), and PPBS was achieved by 63.6% ($P < 0.0001$) versus 42.8% ($P < 0.03$) in the add-on with DPP4 inhibitor versus intensified treatment group. No hypoglycemic episodes were documented in both the groups. Add-on with DPP4 inhibitor cost ($\times 5.13$) as compared to intensified treatment. **Conclusions:** Add-on with DPP4 inhibitor therapy achieved glycemic goals in greater proportion of patients as compared to treatment intensification but at 5 times the cost of therapy. Since the patent restrictions for DPP4 inhibitors such as vildagliptin and teneligliptin are over, the cost of therapy has come down. Hence their benefits should be extended to a greater proportion of patients with inadequately controlled type 2 DM.

Keywords: Cost-effective analysis, diabetes mellitus type 2, DPP4 inhibitors, glycated hemoglobin, glycemic control

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease which requires lifelong pharmacotherapy and lifestyle modifications. India has the largest population of diabetic study patients and ranks second in the world, closely following China.^[1] While diet and lifestyle changes are cornerstone in the management of type 2 diabetes, most if not all study patients eventually require pharmacological interventions to manage hyperglycemia as well as both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (coronary heart disease [CHD], cerebrovascular disease, and peripheral vascular disease).^[2]

To date, there are several guidelines to control and avoid

diabetic complications worldwide. The very recent target to prevent and control diabetic complications is a glycated hemoglobin (HbA1c) $< 7.0\%$ as a target,^[3] which can be achieved through a combination of diet, exercise therapy, and pharmacotherapy to decrease the incidence of microvascular and macrovascular complications without predisposing the patients to hypoglycemia.^[4] However, despite the wide array

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How to cite this article: Kalyani A, Kuchya S, Puneekar P. A single-center, observational, retrospective cost-effective analysis of treating inadequately controlled type 2 diabetes mellitus by addition of dpp4 inhibitors versus intensified treatment with conventional drugs. J Pharmacol Pharmacother 2021;12:125-30.

Received: 22-02-2021 **Revised:** 25-06-2021

Accepted: 04-08-2021 **Web Publication:** 25-11-2021

Access this article online

Quick Response Code:



Website:
www.jpharmacol.com

DOI:
10.4103/jpp.jpp_22_21

of treatment options and guidelines available, chances of hypoglycemia and inadequate glycemic control increased over time.

New therapies with the minimal risk of hypoglycemia and better HbA1c control are now mostly used. Due to the unique mode of action on the glucose concentration and the low risk of hypoglycemia, DPP-4i has attracted a lot of research interests from basic science to clinical trials from pharmacokinetics to pharmacodynamics, including safety and efficacy.^[5] The common practice in recent days is to either intensify the treatment with previously prescribed drugs such as metformin and glimepiride or to add DPP-4i like vildagliptin as add-on therapy when the previous ongoing therapy fails to achieve the target level of glycemic control.^[6-10]

Controlling the cost of treatment is a major issue, as it affects the national budget, and situation is worse in developing countries where resources are limited. Cost-effectiveness analysis (CEA) is used when the effects of the two interventions being compared are different (i.e. one intervention is superior to the other). It requires measuring the cost per defined measurable clinical outcome (effect) for each of the medicines. The cost of the medicine should include indirect as well as direct costs. The cost-effectiveness ratio (CER), or the cost per unit of benefit of the health-care intervention (e.g. medicine), is estimated by dividing the total intervention or medicine cost by the number of units of outcome. The incremental CER (ICER) is the change in costs and health benefits when one health-care intervention (e.g. medicine A) is compared with the alternative intervention (e.g. medicine B).

The formula below demonstrates how the ICER is calculated.

$$\text{ICER} = \frac{\text{Cost of intervention B} - \text{Cost of intervention A}}{\text{Effect of intervention B} - \text{Effect of intervention A}}$$

While newer drugs like DPP4 inhibitor are costlier than older drugs but have a lower risk of weight gain and hypoglycemia.^[11] DPP4 inhibitors have been very often proposed/prescribed as an alternative to treatment intensification with previously prescribed oral hypoglycemic agents (OHAs).

There is no lack of data regarding the cost-effectiveness, safety, and efficacy of the intensified treatment versus add-on with DPP4 inhibitor group in our population, so this study was conducted to compare the cost-effectiveness and achievement of glycemic goals in-between patients receiving intensified treatment and those receiving add-on with DPP4 inhibitor.

MATERIALS AND METHODS

This was a retrospective, observational, and single-center study conducted at the Diabetes Outpatient Department (OPD) at NSCB Medical College, Jabalpur, on inadequately controlled type 2 DM patients who were on treatment with conventional oral hypoglycemic drugs.

A total of 52 patients were included in the current retrospective analysis. The study was conducted with the help of diabetic

diaries containing follow-up from January 1, 2019, to August 31, 2020. Demographic data such as age, gender, and duration of diabetes were collected. The privacy and confidentiality of data were maintained throughout the study period. Data were collected at 3 months and 6 months and were compared with those at baseline levels with appropriate statistical tool [Figure 1].

Here, baseline data were defined as measurements done before the initiation of either intensification of treatment (i.e. increase in the dose of drugs) or add on with DPP4 inhibitor. Change in each study parameter after 3 months of intensification of treatment versus add-on with DPP4 inhibitor, namely (a) HbA1c, (b) fasting blood sugar (FBS), and (c) postprandial blood sugar (PPBS), was compared with the respective baseline parameter. Apart from these, adverse drug reactions like hypoglycemia were noted if any and prices of drugs prescribed were obtained from Drug Price Control Order (DPCO) 2018 price list [Figure 2].

Inclusion criteria

- Individuals more than 30 years of age of both genders
- Those who had inadequately controlled type 2 DM (FBS ≥ 126 , PPBS ≥ 200 , and HbA1c $\geq 6.5\%$)
- Those on therapy with conventional OHAs
- Those who were on continuous follow-up >6 months in the Diabetic OPD.

Exclusion criteria

We excluded the following study individuals in the current study:

- Pregnant and lactating women
- Those on insulin as therapeutic modality
- Renal failure (moderate to severe) – Glomerular filtration rate <60 ml/min
- Anemia
- Thyroid states – Hypothyroidism/hyperthyroidism and other comorbidities which had necessitated the use of insulin.

Statistical analysis

The data were stored, segregated, and processed with the help of computer software MS Excel. For continuous variables, data were represented using means $\pm$ 2 standard deviation (SD). For categorical data, the number and percentage were used in the data summaries. To compare change in glycemic value within the same group at 3 months, 6 months, paired t-test, assuming equal variance were used. The difference between the means of two independent groups was tested by an unpaired t-test, assuming unequal variance. $P < 0.05$ upon two-tailed analysis was considered significant.

RESULTS

A total of 52 patients were included in the current retrospective study, with 7 study patients receiving intensified therapy with previously prescribed drugs and 45 study patients receiving add-on with DPP4 inhibitor.

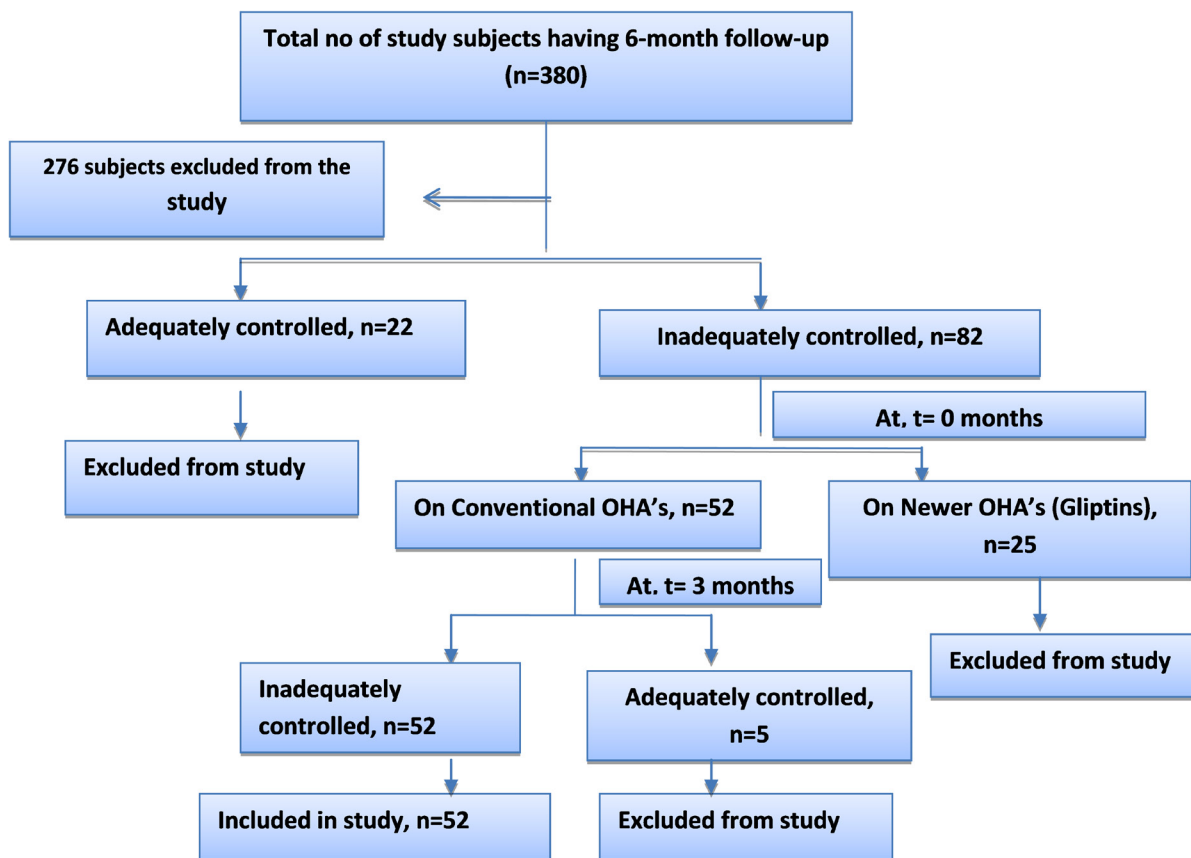


Figure 1: Study flowchart

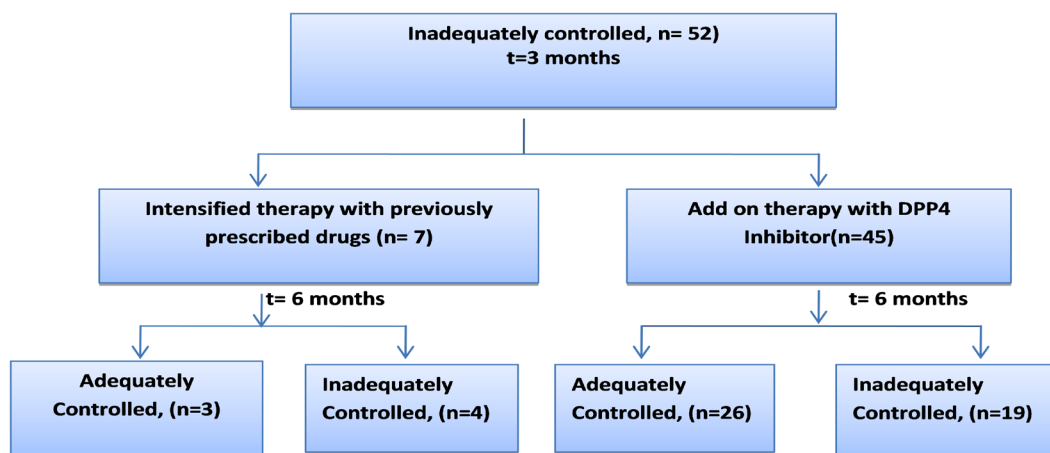


Figure 2: Study flowchart

Within the intensified therapy group, target HbA1c was achieved by 40% ($P < 0.05$), FBS was achieved by 50% ($P < 0.16$), and PPBS was achieved by 42.8% ($P < 0.03$) of the study patients. Within the add-on with DPP4 inhibitor group, target HbA1c was achieved by 58.6% ($P < 0.0001$), FBS was achieved by 78.50% ($P < 0.0001$), and PPBS was achieved by 63.6% ($P < 0.0001$) of the study patients.

Between the intensification and add on with DPP4 inhibitor groups, comparison of mean reduction in FBS (mg/dl) levels were 27.4 ± 18.1 and 60.2 ± 31.8 ($P = 0.02$). The difference was statistically significant. Between the intensification and add on with DPP4 inhibitor, comparison of mean reduction in PPBS (mg/dl) levels were 52.7 ± 7.2 and 71.4 ± 10.7 ($P = 0.22$). The difference was statistically not significant. Between

Table 1: Comparison of fasting blood sugar between intensified verses add-on with dipeptidyl peptidase-4 inhibitor groups

Group (FBS)	3 months	6 months	Mean change	P value within group	P value between the groups
Intensification	168.5±59.2	141.1±41.1	27.4±18.1	<0.16	0.02 (<0.05)
Add-on with DPP4 inhibitor	202.1±62.5	141.9±30.7	60.2±31.8	<0.0001	

FBS (mg/dl) = Fasting blood sugar, DPP4=Dipeptidyl peptidase-4

Table 2: Comparison of postprandial blood sugar between intensified verses add-on with dipeptidyl peptidase-4 inhibitor groups

Group (PPBS)	3 months	6 months	Mean change	P value within group	P value between the groups
Intensification	252±44.0	199.2±51.2	52.7±7.2	<0.03	0.22 (<0.05)
Add-on with DPP4 inhibitor	279±52.7	207.7±42	71.4±10.7	<0.0001	

PPBS (mg/dl) = Postprandial blood sugar, DPP4=Dipeptidyl peptidase-4

Table 3: Comparison of glycated hemoglobin between intensified verses add-on with dipeptidyl peptidase-4 inhibitor groups

Group (HbA1c)	3 months	6 months	Mean change	P value within group	P value between the groups
Intensification	7.08±0.22	6.86±0.15	0.22±0.07	<0.05	0.01 (<0.05)
Add-on with DPP4 inhibitor	7.14±0.5	6.75±0.48	0.37±0.07	<0.0001	

HbA1c=Glycated hemoglobin, DPP4=Dipeptidyl peptidase-4

Table 4: Cost-effective analysis between intensified verses add-on with dipeptidyl peptidase-4 inhibitor groups

Group	n	Total cost for 3-month therapy (Rs.)	Average cost for 3-month therapy (per study patient) (Rs.)	Success rate in terms of HbA1c reduction (%)	CER for study group (Rs.)	ICER, between the groups (Rs.)
Intensification therapy group	7	6289	898	42	14,973	24,780
Add-on with DPP4 inhibitor	45	207,680	4615	57	364,350	

HbA1c=Glycated hemoglobin, DPP4=Dipeptidyl peptidase-4, CER=Cost-effectiveness ratio, ICER=Incremental CER

the intensification and add on with DPP4 inhibitor, comparison of mean reduction in HbA1c (%) levels were 0.22 ± 0.07 and 0.37 ± 0.07 ($P = 0.01$). The difference was statistically significant [Tables 1-3].

The average therapy cost per patient in the intensified treatment group was Rs. 898 versus 4615 for the DPP4 inhibitor group as per DPCO 2018 prices. The ICER, i.e. amount of money needed for HbA1c reduction by 1 unit, stood at Rs. 24,780 in the DPP4 inhibitor arm. The cost of therapy per study patient was five times more in the add-on therapy (with DPP4 inhibitor) group as per DPCO 2018 price list [Table 4]. The current study used only CEA and the cost comprised the direct costs involved in buying the drugs. There was no adverse drug effect reported in any group, So the additional cost for management of adverse effect is not included. Further, the drugs studied were of oral formulations and therefore did not include administration/storage cost.

DISCUSSION

The average age of study patients (52) in the Medicine Diabetic OPD was (mean $\pm$ 2 SD) found to be 52.8 ± 26.4 years similar

to a previous study.^[12] Most of the study patients were having type 2 DM for the last 5 years as higher age was associated with comorbidities such as hypertension, thyroid disorders, coronary heart disease, and others or insulin were started for their treatment and maintenance of glycemic values so they were excluded from the study. The present study aimed at comparing the efficacy, safety, and CEA between intensification of treatment and DPP4 inhibitors as add-on therapy to conventional prescribed drugs in those with inadequately controlled type 2 DM within the group and between the two groups.

The primary goal of treatment is to target glycemic control by maintaining the HbA1c level near 6%–6.5% in order to decrease the incidence of microvascular and macrovascular complications without predisposing study patients to hypoglycemia.^[13] The most frequently used drugs were metformin, glimepiride, and pioglitazone in the study group with intensified therapy, while metformin and vildagliptin were prescribed in the in the DPP4 inhibitor add-on group.

It was observed that mean change in reduction of FBS(mg/dl) is more in the add on with DPP4 inhibitor group, i.e. 60.2 ± 63.6 ,

compared to the intensification group, 27.4 ± 36.2 . There is a significant reduction of FBS ($P \leq 0.02$) between the two groups. The result was similar to those reported by other studies like Gullapalli and Desai in a nonrandomized longitudinal intervention study from Karnataka found that the decrement in mean FBS was significantly more in the vildagliptin group than in the glimepiride group which was similar to their study.^[14] Another study conducted by Chatterjee,^[15] Mitra and Ray,^[5] Charbonnel *et al.*,^[16] and Devarajan *et al.*^[17] showed comparable results.

Change in PPBS (mg/dl) in the intensification group ($P \leq 0.03$) and in the add-on with DPP4 inhibitor group is significant ($P \leq 0.0001$). Mean change in reduction of PPBS is more in the add-on with DPP4 inhibitor group, i.e. 71.4 ± 21.4 , compared to the intensification group, 52.7 ± 14.4 . The result was similar to those reported by other studies like a study by Sarkar *et al.*,^[12] Chatterjee,^[15] Gullapalli and Desai,^[14] Jeon and Oh,^[6] and Sahai *et al.*^[18]

The primary goal of treatment is to target glycemic control by maintaining the HbA1C level near 6.5% to decrease the incidence of microvascular and macrovascular complications without predisposing study patients to hypoglycemia. It was observed that mean change in the reduction of HbA1c is more in the add on DPP4 group, i.e. 0.37 ± 0.14 , compared to the intensification group, 0.22 ± 0.14 . Between the two groups, HbA1c reduction is significant ($P \leq 0.01$). The result was similar to those reported by other studies like Chatterjee,^[15] Charbonnel *et al.*,^[16] Filozof and Gautier,^[19] Muthukrishnan *et al.*,^[20] Kesavadev *et al.*,^[21] and Sahai *et al.*^[18]

The current study used CEA, the cost comprised the direct costs involved in buying the drugs only. there was no adverse drug effect reported in any group, so additional cost for management of adverse effect is not included. Further, the drugs studied were oral, therefore did not include administration/storage, etc., cost. As the investigations were similar in both the arms, the cost for the investigations was not included in the data. The cost of drugs was taken from DPCO 2018 price list. Diabetes, a chronic disease, needs lifelong therapy and hence the cost becomes an important factor in choosing the antidiabetic medication. Other studies by Tandon *et al.*,^[22] George *et al.*,^[23] and Limaye *et al.*^[24] found similar observations.

The study highlighted the need to assess the cost effectiveness of intensified treatment versus add on with DPP4 inhibitors as most of the study patients belongs to economically weaker section. Further studies with a bigger population size, for a longer duration in a prospective manner and possibly in those with one or more comorbidities, too should be conducted.

CONCLUSIONS

It could be concluded from the present study that add-on therapy with DPP4 inhibitor therapy is an effective, well-tolerated option for inadequately controlled type 2 diabetic patients. A higher percentage of patients with add

on DPP4 inhibitor achieved the target glycemic control and showed more reduction in HbA1c%, and this stands out as a better approach. DPP4 inhibitor though has greater benefit but also costs 5 times more than the intensification group. Now that DPP4 inhibitors such as vildagliptin and teneligliptin have come out of patent restrictions, therefore, the price of vildagliptin has come down by almost 80% or even more. Hence, their benefits in terms of better glycemic control should be extended to a greater proportion of inadequately controlled type 2 DM patients.^[11]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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