

# Evaluation of the Cost-Effectiveness of Different Insulin Regimes during the Peri-Operative Period in Type-2 Diabetics in India

MUSHTAQ AHMAD, ZAHOR AHMAD WAFAI, ZAFER YAB KHAN, VIKAS SETH

## ABSTRACT

**Background and Objectives:** Diabetes accounts for at least 10% of the total expenditure in many countries. Diabetics who undergo surgery are prone to adverse outcomes that can prolong their hospital stay and increase their health care expenditure. This prompted the present study to compare the cost-effectiveness of different insulin regimes during the peri-operative period in type 2 diabetics.

**Study Design:** This study was a multi-centric, prospective, single blind, randomised study. Two hundred eighty nine type 2 diabetes mellitus patients who underwent major elective surgeries were enrolled and randomly allocated to four groups A, B, C and D, receiving pre-mixed Regular/NPH(30:70), split-mixed Regular/NPH, split-mixed Glargine/Lispro and split-mixed Detemir/Aspart, respectively.

**Materials and Methods:** Each group received multiple injections from the preoperative to the postoperative period until the patients were switched back to the same treatment regime which they received preoperatively. The starting dose of the insulin was 0.5 units per/kg body weight, which was then adjusted to maintain the average blood glucose level between 120-180mg/dl during the peri-operative period. The cost-effectiveness was calculated

and the interventions were compared on the basis of the amount which was needed to treat the patient. The average one day cost for all the regimes was calculated and the total cost was divided by the percentage of the success of the regime by applying an incremental cost-effectiveness formula. The Chi-square test was employed for analysis of the complications and one way ANOVA was used for the rest of the data. A probability value of less than 0.05 ( $p < 0.05$ ) was considered to be statistically significant.

**Results:** There was a highly significant difference ( $p < 0.001$ ) in the mean costs of the regime A, B, C and D, respectively. The cost-effectiveness was done in a fashion of regime A vs. B and regime C vs. D. The incremental cost of the treatment for regime B was Rs. 7.21 and for regime D, it was Rs. 20.17 per added patient, with no peri-operative complications. However, the percentage of the incidence of the complications and the total cost was comparatively low with regime A.

**Conclusions:** This study found the pre-mixed NPH/regular (30:70) regime to be a cost-effective therapy among the regimes which were compared, while the split-mixed (NPH) regime posed a greater financial burden on the patient in terms of the complications which occurred and the total cost of the treatment.

**Key Words:** Insulin, Type-2 diabetics, Cost-effectiveness, Peri-operative period, Cost, NPH, Lispro, Aspart, Glargine, Detemir

## KEY MESSAGE

- Diabetes accounts for at least 10% of the total health expenditure in many countries.
- India has the world's largest diabetes population that imposes a large economic burden.
- Studies on the cost-effectiveness of the insulin regimes during the peri-operative period in type 2 diabetics are lacking.
- The pre-mixed NPH/regular regime is a cost-effective therapy, while the split-mixed (NPH) regime poses a greater financial burden
- The glargine/lispro and detemir/aspart regimes could be preferable in patients who could afford them, as lesser complications were observed with them.

## INTRODUCTION

The alarming prevalence of type-2 diabetes worldwide in general and in India in particular, poses a major clinical and economic burden. The cost of diabetes care is high and is escalating worldwide. Diabetics have a 50% risk for undergoing surgery in their life span than non diabetics and are more prone to adverse outcomes, resulting in an increase in their health care expenditure [1]. India, a developing country, with limited economical resources, is leading the world in the number of diabetics and lacks a comprehensive

health care system for diabetic patients. Diabetes accounts for at least 10% of the total health expenditure in many countries. Globally, it is the 5<sup>th</sup> leading cause of death. The WHO estimated a figure of about 987000 deaths in the year 2002, directly due to diabetes, which is 1.7% of the total world mortality. The cost of the treatment also depends on the severity of the disease [2]. Higher medical costs were associated with elevated fasting plasma glucose levels [3]. Preventing the progression to diabetes, when the costs are known to be dramatically greater, would be likely to provide substantial

economic benefit [4]. Similarly, a study showed a 26% increase in the financial requirements for diabetes in Mexico from 2003 to 2005 [5]. A WHO report says that excess mortality which is attributable to diabetes, has in the past decade, caused more deaths than all the wars combined [6]. Also, the rates of disability are in general about 2-3 times as great in diabetics than in non-diabetics, but blindness is about 10 times common and gangrene is 20-30 times common in diabetics [7].

The total cost for diabetes in 2010 was forecast to be \$778,427,475, including direct and indirect costs [8]. While comparing the different insulin analogues for cost-effectiveness, the newer, longer acting glargine was found to be comparatively more cost-effective in type-2 diabetes mellitus (DM) patients than its intermediate acting (NPH) counterpart [9]. As against these findings, a study reported pre-mixed 30/70 to be highly cost-effective (88% than glargine) [10]. Another study reported that insulin glargine was associated with an incremental cost of \$642.994 per quality-adjusted life-year [11]. Patients with type 2 diabetes mellitus who were treated with glargine/gulisine achieved better glycaemic control than did patients who were treated with pre-mixed insulin, without an increase in the cost of treatment [12].

Patients with diabetes undergo surgery at a higher rate than non-diabetics and are prone to adverse outcomes that can prolong the hospital stay [13] and increase the mortality [14]. The suboptimal glycaemic management during surgery contributes to increased morbidity and aggravates the untoward effects of concomitant illnesses [15]. To minimize the effects, both of the metabolic derangement on the surgical complications and of the surgery on hyperglycaemia, the management in the peri-operative period depends on the ambient level of glycaemic control and the treatment regimen [16]. Different insulin treatment interventions are employed to control the hyperglycaemia and to reduce the incidence of postoperative complications in type-2 diabetics during the peri-operative period. But studies on the comparative assessment of the cost-effectiveness of the insulin regimes are lacking.

This prompted the present study to find out the cost-effectiveness of different insulin regimes which were given to diabetic patients during their peri-operative period.

## MATERIALS AND METHODS

Two hundred eighty nine type-2 diabetes mellitus patients who underwent major surgeries, who were admitted to the surgical wards, were enrolled. All the patients were referred to the endocrinology unit of the concerned participating hospital for metabolic management. The patients in whom it was decided to control the preoperative hyperglycaemia with subcutaneous insulin were studied. Old and newly diagnosed type-2 DM patients of ages between 18-70 years were included and patients on the concomitant use of oral hypoglycaemics, chronic corticosteroids or any other drug which precipitated or aggravated the diabetes mellitus were excluded. Patients who were undergoing coronary artery bypass grafting surgery and pregnant females were also excluded. This study was conducted at the M.G. hospital, S.M.S. hospital and the Fortis Escorts hospital, Jaipur. Written, informed consents of all the patients and the approval of the institutional ethics committee (IEC) were obtained before the start of the study.

Each group was given multiple injections into the subcutaneous tissue of the upper arm, the anterior and lateral aspects of the thigh and into the buttocks and abdomen preoperatively till a day before the surgery and a day after the surgery, until the patients

were switched back to the same treatment regime which they received preoperatively. The starting dose of the insulin was 0.5 units per/kg body weight. The insulin dose was adjusted according to the pre-meal and post-meal blood glucose values. Any increase or decrease in the insulin requirement was noted and compared with a goal to maintain the average blood glucose level between 120-180mg/dl. In split-mixed regimes, regular insulin was given (SC) in three equally divided doses, with each meal and long acting insulin being administered regardless of the patient's oral intake status at bed time. The pre-mixed regime was given twice daily, before breakfast and before dinner. The blood glucose (BG) was measured before each meal and at bed time to assess the glycaemia control. In addition, the BG was measured at any time if a patient experienced the symptoms of hypoglycaemia (BG<60 mg/dl) or if it was requested by the treating physician. The outcomes which were observed were the differences in the degree of glycaemic control and the incidence of the postoperative complications which occurred among the treatment groups. The total costs were categorised as the direct and indirect costs of each patient were calculated and then, the cost-effectiveness of the insulin regimes were compared.

The cost-effectiveness was calculated and the interventions were compared on the basis of the amount which was needed to treat the patient. Initially, for all the treatment regimes, the average one day cost was calculated. Then, the total cost of the hospital stay from admission to discharge was calculated. The total cost was divided by the percentage of the success of the regime (i.e. the percentage of patients who had no complications by the particular treatment regime) by applying the Incremental Cost-Effectiveness (ICE) formula [17].

$$ICE = \frac{(\text{Cost of Treatment A} - \text{Cost of Treatment B})}{(\text{Success of Treatment A} - \text{Success of Treatment B})}$$

**Statistical Analysis:** The Chi-square test was employed for the analysis of the complications and ANOVA (one way classification) was used for the rest of the data. The statistical analysis was done by the SPSS version 10.0 statistical software. A probability value of less than 0.05 ( $p < 0.05$ ) was considered to be statistically significant.

## RESULTS

All 289 type-2 diabetes mellitus patients who were operated for different major surgical procedures completed the study. The four treatment groups were comparable with respect to age, sex and BMI. The patients were compared on the basis of the insulin dose, the days of hospitalization and the cost and incidence of the postoperative complications which were attributable to the treatment regimes during the peri-operative period [Table/Fig-1]. Then, the total cost of the hospital stay from admission to discharge and the effectiveness i.e. the percentage of patients with no postoperative complications (NPOC) were calculated to assess the cost-effectiveness of each treatment regime. The mean pretreatment blood glucose levels in treatment regime A ( $232.10 \pm 3.90$ ), B ( $229.05 \pm 3.61$ ), C ( $233.71 \pm 5.31$ ) and D ( $227.76 \pm 5.61$ ) were similar among the treatment groups ( $P = \text{NS}$ ).

While comparing the mean total daily insulin dose, it was found that there was a highly significant difference ( $p < 0.001$ ) in the treatment regimes A ( $37.36 \pm 0.82$ ), B ( $36.24 \pm 0.97$ ), C ( $30.46 \pm 1.44$ ), and D ( $31.50 \pm 0.63$ ), respectively. However, the mean total insulin

Variable	Group				P-value
	A Premixed Regular + NPH	B Split-mixed NPH + Regular	C Split-mixed Glargine + Lispro	D Split-mixed Detemir + Aspart	
n	74	75	69	71	–
Age (yr)	58.36 ± 0.80	55.60 ± 1.44	52.49 ± 1.37	63.50 ± 1.05	–
Insulin dose (units/day)	37.36 ± 0.82	36.24 ± 0.97	30.46 ± 1.44	31.50 ± 0.63	< 0.001
Mean days hospitalized	8.17 ± 0.46	6.81 ± 0.38	5.73 ± 0.18	6.7 ± 0.10	<0.001
Mean cost	448.90 ± 28.99	501.78 ± 36.99	641.27 ± 28.92	861.64 ± 25.4	<0.001
% with no postoperative complication	50%	57.33%	62.31%	73.23%	–

[Table/Fig-1]: Comparison of parameters in patients receiving different insulin regimes

dose which was used to achieve the target was comparatively lower in regime C. On comparing the mean number of days of hospitalization; a significant difference was observed in the mean number of days of hospitalization in the regimes A (8.17 ± 0.46), B (6.81 ± 0.38), C (5.73 ± 0.18), and D (6.7 ± 0.10), respectively. However, the patients of regime C took lesser time and had an earlier recovery as compared to those who received the other regimes.

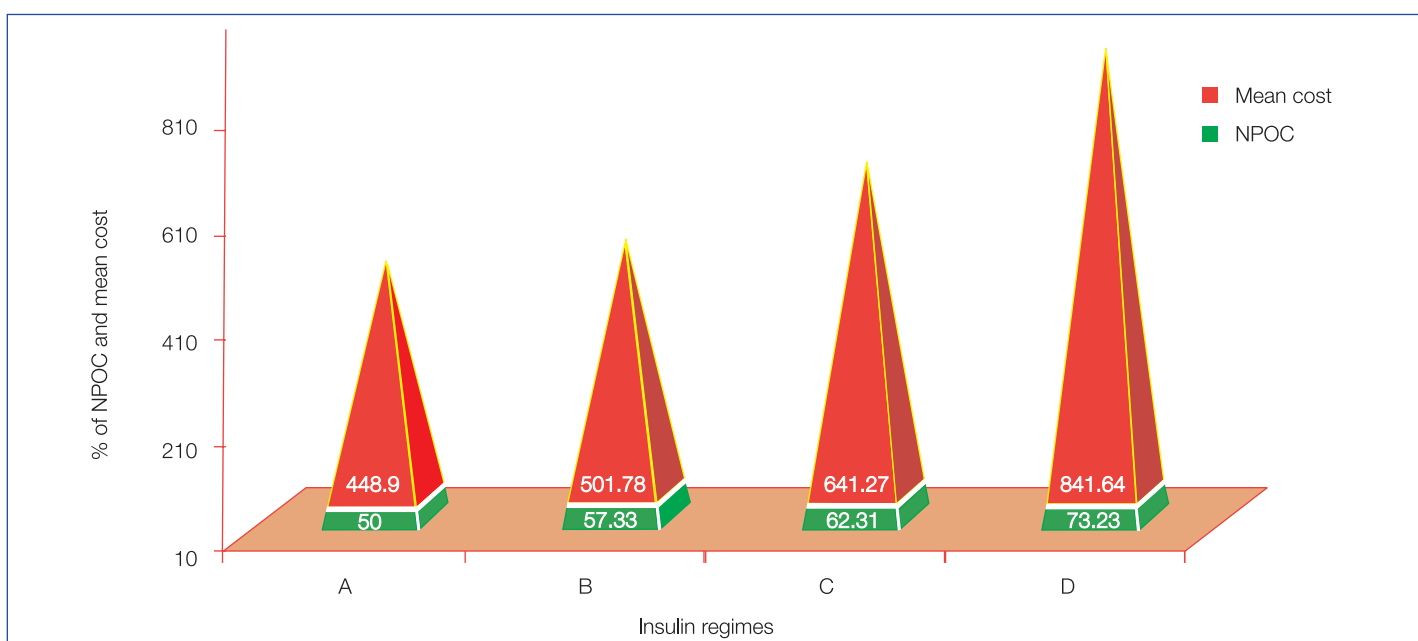
On comparing the mean cost of the insulin regimes which were used during the peri-operative period, it was found that there was highly significant difference ( $p < 0.001$ ) among the regimes A (448.90 ± 28.99), B (501.78 ± 36.99), C (641.27 ± 28.92) and D (861.64 ± 25.4) respectively. However, the mean cost was comparatively lower in patients who were treated with regime A. While comparing the percentage of the patients who had no postoperative complications (NPOC), it was found that 50% of the patients had no complications with regime A, 57.33% had no complications with regime B, 62.31% patients had no complications with regime C and 73.23% patients had no complications with regime D [Table/Fig-2].

The mean cost of each insulin regime which was given during the peri-operative period and the treatment effectiveness i.e. the percentage of patients with no postoperative complications (NPOC) were compared for the cost-effective analysis (CEA) in a fashion of regime A vs. B and regime C vs. D. The incremental cost of the treatment regime B was Rs. 7.21 and for regime D, it was Rs. 20.17 per added patient, with no postoperative complications.

Though the cost of the regime A was comparatively less with 50% of the patients having no postoperative complications, resulted as cost-effective regime among regimes compared [Table/Fig-3]. However, the higher number of patients (73.23%) who received the insulin regime D had no postoperative complications (NPOC), though the cost factor was higher as compared to those who received the other insulin regimes.

## DISCUSSION

The economic comparison with regards to the use of the treatment interventions for cost-effectiveness becomes more relevant today while considering the magnitude of the problem, the money spent on it and the increasing prevalence of diabetes mellitus in the developing countries with limited resources. India is leading the world in the number of diabetics and this number would increase to 80 million diabetic patients by the year 2030 [18]. One fifth of the patients who undergo surgery are diabetics [1]. Different insulin treatment regimes are used for glycaemic control to avoid postoperative complications. Apart from the efficacy and safety, the affordability of the treatment regime is equally important for a patient from the low socioeconomic strata. There is a paucity of studies which have compared the different insulin regimes for cost-effectiveness in type-2 diabetics during the peri-operative period. However, studies on non surgical clinical situations are available. This study has compared four different insulin regimes in type-2 diabetes mellitus patients who underwent different major surgical procedures during their peri-operative period. The major outcomes which were



[Table/Fig-2]: Mean cost and percentage of patients with no postoperative complication (NPOC) using different insulin regimes.

Abbreviations: A = Regular + NPH 30:70 (Pre-mixed), B = Regular + NPH (split-mixed), C = Glargine + lispro (split-mixed), D = Detemir + aspart (split-mixed), NPOC = No postoperative complication

Regime	Regime A vs. B and C vs. D		
	Cost (Mean + SEM) (Rs)	Success of the Regime (Patients having no complications)	Incremental cost-effective- ness ratio (ICER)
A	448.90 ± 28.99	37 (50%)	B = 7.21
B	501.78 ± 36.99	43 (57.33%)	
C	641.27 ± 28.92	43 (62.31)	D = 20.17
D	861.64 ± 25.4	52 (73.23%)	

**[Table/Fig-3]:** Cost- effectiveness of the regime A vs. B and C vs. D  
Abbreviations: A = Regular + NPH 30:70 (Pre-mixed), B= Regular + NPH (split-mixed), C = Glargine + Lispro (split-mixed), D = Detemir + Aspart (split-mixed)

compared for the evaluation of the cost-effectiveness were the costs which were spent from admission to discharge on the medication, hospital stay and the incidence of the postoperative complications in each insulin regime which was given to the patient groups during the peri-operative period. For the evaluation of the incremental cost-effective ratio (ICER) [19], the group A which received premixed NPH/regular in a ratio of 30:70 was compared with the group B who received split-mixed NPH/regular, while group C which received split-mixed glargine/lispro was compared with regime D which received split-mixed detemir/aspart, respectively.

The regimes A, B, C and D showed a significant difference ( $p < 0.001$ ) in the average insulin dose which was used during the peri-operative period. However, the total insulin dose which was used during the peri-operative period was comparatively low in patients who received the basal bolus insulin regime C (glargine/lispro). While comparing the mean number of days for which the patients were hospitalized, who received the different insulin regimes, it was found that there was a significant difference ( $p < 0.001$ ) among all the regimes. However, the hospital stay was less in patients who received the insulin regime C (glargine/lispro) as compared to those who received the other insulin regimes. On assessing the entire cost which was spent on the medication and the hospital stay for the analysis of the cost-effectiveness of the insulin regimes, it was found that there was a highly significant difference ( $p < 0.001$ ) in the regimes A, B, C and D, respectively. The mean cost was comparatively lesser in patients who received regime A (premixed NPH/regular).

Effectiveness, an important domain of the incremental cost-effective ratio (ICER), was analysed by the percentage of the patients who had no postoperative complications (NPOC) with the insulin regime that they received during the peri-operative period. The least number of patients (50%) with NPOC who received premixed NPH/regular (30:70) were recorded in group A. It was interesting to note that a higher percentage of patients with NPOC were recorded in the basal bolus regimes of glargine/lispro (62.31%) and the highest number (73.23%) with NPOC were recorded in regime D (detemir/aspart).

On comparing the analysis of the mean cost and the percentage of NPOC which was achieved by the different insulin regimes for the incremental cost-effective ratio (ICER), the ICER was found to be Rs. 7.21 per added patient with no peri-operative complications, with the treatment regime B (split-mixed NPH/regular). While comparing the basal bolus regime C vs. regime D, the ICER was found to be Rs. 20.17 per added patient with no peri-operative complications, with regime D (detemir/aspart). The NPH/regular regimes were cost-effective as compared to the basal bolus glargine/lispro and the detemir/aspart. However, this study, as is evident from the

results, found out that the pre-mixed NPH/regular (30:70) regime was a cost-effective therapy as compared to the other insulin regimes. The results of this study are in support of a medical study which reported premixed NPH/regular (30:70) to be highly cost-effective (88% than glargine) [10]. Another study reported similar results, that premixed NPH/regular was cost-effective in UK settings in comparison to insulin glargine [20]. On the contrary, a study on type 2 diabetics reported glargine/gulisine to be more cost-effective than premixed NPH/regular [12].

Though the cost factor was low in the NPH/regular regimes, the complications which were observed were much lesser with the basal bolus regimes of glargine/ lispro and detemir/aspart. Therefore, the glargine/lispro and detemir/aspart regimes could be preferable in patients who could afford them. With the advent of newer analogues of insulin, more short and long term studies are needed in this direction to establish the cost-effectiveness of the various insulin regimes.

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**AUTHOR(S):**

1. Dr. Mushtaq Ahmad
2. Dr. Zahoor Ahmad Wafai
3. Dr. Zafer Yab Khan
4. Dr. Vikas Seth

**PARTICULARS OF CONTRIBUTORS:**

1. Department of Pharmacology, Mahatma Gandhi Medical College & Hospital, Sitapura, Jaipur- 302022.
2. Department of Clinical Pharmacology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar (Jammu & Kashmir) State - 190001.
3. Department of Pharmacology, Mahatma Gandhi Medical College & Hospital, Sitapura, Jaipur- 302022.
4. Department of Pharmacology, Mahatma Gandhi Medical College & Hospital, Sitapura, Jaipur- 302022.

**NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Dr. Mushtaq Ahmad  
Assistant Professor, Department of Pharmacology  
Mahatma Gandhi Medical College & Hospital,  
Sitapura, Jaipur-302022.  
Phone: 9460983755;  
E-mail: marumush@gmail.com

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