International Journal of Research in Medical Sciences
Halder S et al. Int J Res Med Sci. 2016 Sep;4(9):4014-4021
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20162926

Research Article

Basal-bolus insulin therapy during switching over from continuous intra venous regular insulin to sub cutaneous insulin therapy as compared to conventional regimens in type-2 diabetes patients admitted in intensive care unit

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Received: 11 July 2016
Revised: 12 July 2016
Accepted: 11 August 2016

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ABSTRACT

Background: According to the World Health Organization (WHO), over 347 million people worldwide have diabetes. Latest estimates reveal that 25.4 million Americans have diabetes mellitus (DM), with up to 95% of those having type 2 DM. This study was done to know the effects of Glargine insulin plus human regular insulin on blood sugar control while switching over from continuous IV insulin infusion to SC route as compared to conventional SC insulin regimens in CCU setup.
Methods: 65 patients of T2DM were included this study. Detailed history, physical examination and relevant systemic examination were performed and necessary lab investigations were done.
Results: The mean age was 49.52±10.16. Mean FPG on 1st Day: The p value of B-B against PRE is significant. Mean FPG on Day of discharge: The p value of B-B against PRE is significant and B-B against NPH is also significant. Mean FPG 2Weeks after discharge: The p value of B-B against PRE is significant and B-B against NPH is also significant. Mean PPPG on 1st Day: The p value of B-B against NPH is significant. Mean PPPG on day of discharge: The p value of B-B against PRE is significant. Mean PPPG 2weeks after discharge: The p value of B-B against PRE is significant. Hypoglycemia was occurring in 25, 15, and 25 in BB, NPH, and PRE group respectively. The p value is significant when NPH compared to PRE.
Conclusions: B-B regimen was better than other regimen for controlling FPG and PPPG. The insulin dose was high in NPH regimen compared to both B-B and PRE regimens.

Keywords: T2DM, Fasting plasma glucose, Post prandial plasma glucose, Basal- bolus, NPH, Premix insulin, Hypoglycemia

INTRODUCTION

According to the World Health Organization (WHO), over 347 million people worldwide have diabetes. Latest estimates reveal that 25.4 million Americans have diabetes mellitus (DM), with up to 95% of those having type 2 DM. Additionally, close to 50 million individuals have prediabetes, with an annual conversion rate to diabetes close to 15%. A large component of medical expenditure on diabetes is attributed to hospital inpatient care.[1] In India, the average annual direct costs of hospitalized patients are estimated to be more than double

to those not hospitalised.[1] Type 2 DM is typically characterized by insulin deficiency, coupled with insulin resistance. Continuing declining b-cell function is a hallmark of the disease leading to progressive insulinopenia and persistent carbohydrate and lipid abnormalities. Blood glucose (BG) levels >200 mg/dl are associated with an increase in complications, length of stay and mortality in patients admitted with infections, congestive heart failure, myocardial infarction andstroke.[2] Approximately, 25-40% of hospitalized patients have underlying diagnosis of diabetes. In critically ill-patient populations, approximately 50% of patients experience hyperglycemia.[3]

Despite the well-documented negative impact of uncontrolled hyperglycemia on both early and late morbidity and mortality, controversy remains regarding appropriate glycemic targets as well as the methods for achieving these targets.[4] Much of this controversy stems from the observation of a higher incidence of severe hypoglycemia, defined as BG levels <40 mg/dl that were observed with intensive protocols using intravenous (IV) insulin infusions to achieve what has been defined as "tight" glycemic targets of 80-110 mg/dl.[5]

Despite modifications of recommendations for glycemic targets in critically ill- and non-critically ill-patient populations, concern for hypoglycemia has resulted in variability in in-patient glycemic management strategies.

In patients with T2D admitted to general medicine and surgery services, recent randomized, controlled trials have shown that treatment with a basal-bolus regimen results in significantly lower mean daily blood glucose (BG) and in a higher percentage of BG within target range than does treatment with sliding scale regular insulin (SSI).[6]

A randomized control trial (RCT) conducted in 2001 by Van den Berghe G et al reported that critically ill patients whose blood glucose was maintained at 70-110 mg/dl (3.9-6.12 mmol/L) had a decrease in morbidity and mortality.[7] The study was restricted to surgical intensive care patients. Despite the study being conducted on a very select patient population, this landmark study is said to have launched a new interest in the development of inpatient glycemic control, which continues today.[8]

In 2000, a new type of basal insulin to be administered once daily, in the evening, was approved for use by the US Food and Drug Administration.

Use of this insulin grew in the outpatient clinic setting and in 2003 it was approved for administration at any time of the day. Hyperglycemia in in-patients can have three possible causes which include existing recognized diabetes, existing but unrecognized diabetes and hospital associated diabetes which can be iatrogenic or stress induced.[9] The association between hyperglycemia in hospitalized patients (with or without diabetes) and increased risk for complications and mortality is well established.[10] A retrospective study (July to October 1998) conducted in a community teaching hospital in US to determine the prevalence and mortality of in-hospital hyperglycemia in patients with and without a history of diabetes, found that newly discovered hyperglycemia was associated with higher in-hospital mortality rate (16%) than those with prior history of diabetes (3%) or normoglycemia.[10]

Further, it was observed that new hyperglycemic patients had a longer hospital stay, higher admission rate to an intensive care unit (ICU), and were less likely to be discharged to home, frequently requiring transfer to a transitional care unit or nursing home facility.

A retrospective analysis of patient records (during 2007) from a tertiary care hospital in India reported that diabetes contributed to 8.2% hospitalizations and 15.6% in-patient deaths. This corresponds to mortality rates of 48.3/1000 and 23.4/1000 admissions for patients with and without diabetes, respectively.[11] In this study during switching over from continuous intra venous insulin to sub cutaneous insulin therapy, the Basal-Bolus insulin therapy will be compared to conventional SC insulin therapy in general ICU.

METHODS

All patients of Type 2DM admitted in CRITICAL CARE UNIT who fulfilling inclusion and exclusion criteria are included to my study. This study was undertaken over a period of one and half year. 65 patients were included in this study. Valid consent was taken from all the patients who were included this study. Proper history from all patients was taken and relevant examination of all systems was done. According the patients profile relevant investigations (Like FPG, PPPG etc.) were done. All data were then analyzed statistically.

Inclusion criteria

All critically ill Type 2 DM patients requiring continuous i.v. infusion of regular insulin planned for switching over to S.C. insulin.

Exclusion criteria

Unstable vitals because of which requisite time of observation may not be permitted.

Study design

Type 2 DM critically ill patients in critical care unit who were in IV insulin need transition from IV insulin to SC insulin were selected. We divided the patients into three groups randomly. One group take S.C. mixed insulin (30/70) before breakfast & before dinner, another group single glargine S.C. bolus insulin followed by S.C.1-3 doses of regular insulin and 3rd group with NPH insulin.

Transition guideline

- Conversion to subcutaneous insulin should be delayed until the patient is able to eat and drink without nausea or vomiting & stable.
- The blood sugar is stable & <200mg/dl for last 4hrs on i.v. insulin.
- There should be an overlap between the i.v. insulin infusion and the first injection of fast acting insulin.
- The fast acting insulin should be injected subcutaneously with the meal and the intravenous insulin and fluids discontinued 30 to 60 minutes later.
- The long acting (glargine) insulin should be given S.C. 2hrs before discontinuation of i.v insulin infusion.
- For patients to be on twice daily fixed mix (30/70) regimen. The insulin should be re-introduced either before breakfast or before the evening meal. The i.v insulin infusion should be maintained for 30-60 minutes after the subcutaneous insulin has been given.

Table 1: Protocol for conversion from continuous i.v. insulin and glucose infusion to SC insulin and oral diet.

Protocol	Example
Step 1. Calculate the average insulin intravenous infusion rate in the last 12 h to obtain the mean hourly rate and multiply by 24 to get the total daily insulin requirement.	→ 1.5 units/h × 24 = 36 units/24 h
Step 2. Halve this 24-h insulin dose to obtain the long-acting insulin analog dose and total daily short-acting insulin/ analog dose.	→ 36 units/2 = 18 units
Step 3. Give the long-acting insulin analog subcutaneous monodose 2 h before the first meal and the discontinuation of intravenous insulin and intravenous glucose infusions.	→ give glargine 18 units s.c. 2 h before the first meal and stop intravenous insulin and glucose infusions at meal
Step 4. Split the total daily rapid-acting subcutaneous insulin analog dose into 20% at breakfast, 40% at lunch, and 40% at dinner, according to a similar distribution of carbohydrates in the typical diet.	→ give regular insulin 4 units s.c. before breakfast, give 7 units s.c. before lunch, give7 units s.c. before dinner

Basal Insulin adjustment can be carried out as below:

- If the fasting and predinner BG =140-180 mg/dl (and absence of hypoglycemia) increase dose of basal insulin by 10% every day
- If the fasting and predinner BG >180 mg/dl (and absence of hypoglycemia) increase dose of basal insulin by 20% every day
- If patient develops hypoglycemia (BG <60 mg/dl), decrease basal insulin (detemir) dose by 20%

Table 2: Correction dose for pre-prandial or random hyperglycemia.

Glucose mg/dL	High insulin sensitivity <40 units/day	Average insulin sensitivity 40-80 units/day units insulin to administer	Low insulin sensitivity >80 units/day
<60	-	-3	-4
60-99	2	-2	-2
100-139	-1	No change	
140-200	1	1	2
201-250	2	3	4
251-300	3	5	7
301-350	4	7	10
>350 attending	5 & call	8 & call attending	12 & call attending

RESULTS

The mean age (mean±SD) of patients was 49.52±10.16 years with range 34.00-72.00 years and the median age was 48 years. Percentage of male (52.3%) is more than that of female (47.7%), but not so significantly. Weight in Kgs: B-B group mean 69.0400 and SD 8.5658, NPH group mean 77.0667 SD 7.2157, PRE group mean 71.2800 SD 9.044. Weight difference of three groups was statistically significant (p=0.0183).

Mean Height in Cms: B-B Group Mean154.7600 SD 10.9441, NPH Group Mean 161.4000 SD 8.6915, PRE group mean 157.6000 SD 8.2664. Height difference of three groups was not statistically significant (p=0.1077). Mean BMI kg/m^2: B-B Group Mean 28.8480 SD 2.1376 NPH group mean 29.6000 SD 1.8303 PRE group mean 28.7920 SD 1.9811. BMI difference of three groups was not statistically significant (p=0.4229).

Mean FPG (mg/dl) on 1stDay of S.C Regimen: B-B Group Mean 145.8800 SD 8.5893, NPH group mean 144.5333 SD 11.6978, PRE group mean 153.2400 SD 12.7876. The p value (0.014) of B-B against PRE is significant. The p value (0.244) of B-B against NPH is not significant (Table 3).

Table 3: Mean FPG (mg/dl) on 1st day of S.C regime.

Group	Mean	SD	Minimum	Maximum
B-B	145.8800	8.5893	133.0000	166.0000
PRE	153.2400	12.7876	136.0000	175.0000
NPH	144.5333	11.6978	126.0000	163.0000

The p value (0.014) of B-B against PRE is significant; the p value (0.244) of B-B against NPH is not significant.

Mean FPG (mg/dl) on Day of discharge on S.C. Regimen: B-B Group Mean 121.8000 SD 12.1072, NPH group mean 129.2667 SD 15.4941, PRE group mean 140.6400 SD 14.0650. The p value (<0.001) of B-B against PRE is highly significant. The value (<0.001) of B-B against NPH is highly significant (Table 4).

Table 4: Mean FPG (mg/dl) on day of discharge on S.C. regimes.

Group	Mean	SD	Minimum	Maximum
B-B	121.8000	12.1072	100.0000	142.0000
PRE	140.6400	14.0650	116.0000	163.0000
NPH	129.2667	15.4941	102.0000	151.0000

The p value (<0.001) of B-B against PRE is highly significant; the pvalue (<0.001) of B-B against NPH is highly significant.

Mean FPG (mg/dl) 2Weeks after discharge on S.C. Regimen: B-B Group Mean 104.9600 SD 11.7206, NPH group mean 110.6000 SD21.5566, PRE group mean 129.7200 SD 14.0520. The p value (<0.001) of B-B against PRE is highly significant. The p value (0.004) of B-B against NPH is highly significant (Table 5).

Table 5: Mean FPG (mg/dl) 2 weeks after discharge on S.C. regimes.

Group	Mean	SD	Minimum	Maximum
B-B	104.9600	11.7206	78.0000	125.0000
PRE	129.7200	14.0520	110.0000	151.0000
NPH	110.6000	21.5566	68.0000	141.0000

The p value (<0.001) of B-B against PRE is highly significant; the p value (0.004) of B-B against NPH is highly significant.

Table 6: Mean PPPG (mg/dl) on 1st day of S.C. regimes.

Group	Mean	SD	Minimum	Maximum
B-B	188.8400	11.4807	167.0000	210.0000
PRE	189.4800	10.8325	164.0000	210.0000
NPH	184.8000	15.9562	151.0000	214.0000

The p value (0.351) of B-B against PRE is not significant; the p value (0.050) of B-B against NPH is significant.

Mean PPPG (mg/dl) on 1st Day of S.C. Regimen: B-B Group Mean 188.8400 SD 11.4807, NPH group mean184.8000 SD15.9562, PRE group mean 189.4800 SD 10.8325. The p value (0.351) of B-B against PRE is not significant. The p value (0.050) of B-B against NPH is significant (Table 6). Mean PPPG (mg/dl) on day of discharge on S.C. Regimen: B-B Group Mean 165.0400 SD16.8856, NPH group mean164.6000 SD18.7037, PRE

group mean 170.0000 SD 16.3095. The p value (0.043) of B-B against PRE is significant. The p value (0.203) of B-B against NPH is not significant (Table 7). Mean PPPG (mg/dl) 2 weeks after discharge on S.C. Regimen: B-B Group Mean142.8800 SD12.9013, NPH group mean144.5333 SD20.5387, PRE group mean 153.6800 SD 14.2558. The p value (0.008) of B-B against PRE is significant. The p value (0.083) of B-B against NPH is not significant (Table 8).

Table 7: Mean PPPG (mg/dl) on day of discharge on S.C. regimes.

Group	Mean	SD	Minimum	Maximum
B-B	165.0400	16.8856	138.0000	196.0000
PRE	170.0000	16.3095	144.0000	207.0000
NPH	164.6000	18.7037	127.0000	192.0000

The p value (0.043) of B-B against PRE is significant; The p value (0.203) of B-B against NPH is not significant.

Table 8: Mean PPPG (mg/dl) 2weeks after discharge on S.C. regimes.

Group	Mean	SD	Minimum	Maximum
B-B	142.8800	12.9013	128.0000	180.0000
PRE	153.6800	14.2558	134.0000	182.0000
NPH	144.5333	20.5387	107.0000	180.0000

The p value (0.008) of B-B against PRE is significant; the p value (0.083) of B-B against NPH is not significant.

FPGmg/dl on 1st day of S.C. Regimen. (FBS1): FBS > 140 were 17, 8, and 20 in BB, NPH, and PRE group respectively. FBS ≤ 140 were 8, 7, 5 in BB, NPH, PRE group respectively. (FBS1) [>140 and ≤140] in three regimes shows no significance (p=0.2061).

PPPS (mg/dl) on 1st day of S.C. Regimen (PPBS1): PPBS > 180 were 19, 9, and 19 in BB, NPH, and PRE group respectively, PPBS ≤ 180 were 6, 6, and 6 in BB, NPH, and PRE group respectively.

Table 9: Hypoglycaemic events in each regime.

	Regime			
Hypoglycaemic events	B-B	NPH	PRE	Total
0	23	11	25	59
Row %	39.0	18.6	42.4	100.0
Col %	92.0	73.3	100.0	90.8
1	2	4	0	6
Row %	33.3	66.7	0.0	100.0
Col %	8.0	26.7	0.0	9.2
Total	25	15	25	65
Row %	38.5	23.1	38.5	100.0
Col %	100.0	100.0	100.0	100.0

The p value (0.0180) is significant when NPH compared to PRE separately, but when compared to B-B p-value (0.109) not significant, B-B compared to PRE is p-value (0.149) is not significant.

(PPBS1) [>180 and ≤180] in three regimes shows no significance (p=0.4783). FPG (mg/dl) on the day of discharge on S.C. Regimen (FBS-2): FBS > 140 were 1, 3, 12 in BB, NPH, PRE group respectively, FBS ≤ 140 were 24, 12, and 13 in BB, NPH, and PRE group respectively. (FBS-2) [>140 and ≤140] in three regimes shows significance (p=0.0013) PPPS mg/dl on the day of discharge on S.C. Regimen (PPBS2): PPBS > 180 were 4, 4, and 5 in BB, NPH, and PRE group respectively, PPBS <= 180 were 21, 11, and 20 in BB, NPH, and PRE group respectively. (PPBS2)[>180&≤180] in three regimes shows no significance (p=0.7165). FPG mg/dl 2wks after discharge on S.C.Regimen (FBS-3): FBS > 140 were 0, 1, 10 in BB, NPH, PRE group respectively, FBS ≤ 140 were 25, 14, and 15 in BB, NPH, and PRE group respectively. (FBS-3) [>140 and ≤140] in three regimes shows significance (p=0.0004). PPPG mg/dl 2wks after discharge on S.C. Regimen (PPBS-3): PPBS > 180 were 11, 9, and 18 in BB, NPH, and PRE group respectively, PPBS ≤180 were 14, 6, and 7 in BB, NPH,

and PRE group respectively. (PPBS-3) [>180 and ≤180] in three regimes shows no significance (p=0.1317).

Mean Daily dose of insulin (U/d) in each Regimen: B-B Group Mean 46.3200 SD7.3526, NPH Group Mean58.0000 SD 5.0000, PRE Group Mean 42.8400 SD 5.8144.The p value is very significant with NPH compared to B-B and PRE separately but not significant when compared between B-B and PRE (p=0.065).

Hypoglycemic events in each regimen: Hypoglycemia was occurring in 25, 15, and 25 in BB, NPH, and PRE group respectively. The p value (0.0180) is significant when NPH compared to PRE separately, but when compared to B-Bp-value (0.109) not significant, B-B compared to PRE is p-value (0.149) is not significant (Table 9).

DISCUSSION

A total of 65 type 2DM patients admitted in C.C.U were taken who were on i.v. insulin infusion and were planned for transition to s.c. insulin as per the protocol mentioned in methods. 25 patients got Basal-Bolus insulin therapy, 25 patients got Premixed (30/70) insulin, 15 patients got MSII regime with NPH insulin twice daily.

Table 10: Insulin regimen and systemic involvement of patients.

Medical	B-B	PRE	NPH
Cardiovascular	4 (16%)	4 (16%)	5 (34%)
Neurology	3 (12%)	5 (20%)	2 (13%)
Infections	8 (32%)	9 (36%)	5 (33%)
Metabolic	4 (16%)	3 (12%)	1 (7%)
Pulmonary	3 (12%)	3 (12%)	2 (13%)
Surgical	3 (12%)	1 (4%)	0
Total	25	25	15

There were no significant differences among groups in mean age, BMI, sex and age vs. sex distribution.

Discussion can be done in several headings as follows:-

Basal-bolus vs MSII with NPH twice daily

- In this study the FBS on the day of discharge and 2 weeks after discharge in B-B compared to NPH had p-value (<0.001) and (0.004) respectively. PPBS on the 1st day of regime had p-value (0.05) in favour of B-B. So the FBS was better controlled in B-B than NPH and also PPBS.
- Riddle et al demonstrated greater number of patients reached the target FBS in Glargine group compared to NPH (p<0.03).[12]
- Rosenstock et al compared once daily Glargine with twice daily NPH, % of patients achieving target FBS was significantly higher in Glargine group.[13]
- Yki-Jarvinen et al (LANMET study) determined that Glargine improved pre and post dinner glucose concentrations than NPH[14]
- Fritsche et al demonstrated better glycemic control with Glargine compared to NPH.[15]
- In this study total mean daily dose of insulin required in B-B was compared with NPH.In B-B and NPH mean dose of insulin (min. insulin & max. insulin) are 46.32u/d (35 and 65) and 58u/d (52 and 70) respectively. So insulin dose is lower in Glargine compared to NPH.
- Rosenstock et al also found that insulin dose was lower in Glargine group than NPH (62 vs 72u/d).[13]
- Occurrence of hypoglycemia was compared, B-B 2 out of 25 (8%) and NPH 4 out of15 (27%). None of the hypoglycemic events were <40 and required hospitalization. The hypoglycemic readings were 60-70mg/dl. Compared to B-B, NPH had more hypoglycemic events and p-value (0.109) is not significant.
- Riddle et al found mean yearly rates of symptomatic hypoglycemia significantly higher in NPH group.[12]
- Yki-Jarvinen et al (LANMET study) also determined that Glargine resulted in less nocturnal hypoglycemia than NPH.[14]

Basal-bolus vs premixed (30/70) (BBF&BD) daily

- In this study FBS in B-B compared to PRE on 1st day, day of discharge, 2 weeks after discharge has p-value of (0.014), (<0.001) and (<0.001) respectively. The PPBS in B-B compared to NPH on day of discharge and 2weeks after discharge has p-value (0.043) and (0.008) respectively. So both FBS and PPBS are better controlled in B-B than PRE.
- Raskin et al (INITIATE study), Janka et al (LAPTOP study) showed significant lowering of FBS and achieving target FBS in Glargine group compared to PRE group.[16,17] These studies showed lowered PPBS with PRE group than Glargine as the Glargine group was not covered with prandial regular insulin but was combined with OHA.
- In very few direct comparisons between B-B and PRE Rosenstock J et al, Fritsche A et al, (GINGER study), the B-B group had better FBS & PPBS target achievement.[15]
- Holman RR et al (4T trial) confirmed the superiority of B-B.[18]
- DURABLE study premixed insulin compared with Glargine showed better glycaemic control in the PRE group, as Glargine was combined with OHA & had no prandial insulin coverage.[19]
- In this study the p-value is (0.065) when the total mean daily dose of insulin is compared between B-B and PRE groups. This p-value is not significant.
- Raskin et al (Initiate study) Janka et al (Laptop study), durable study Showed significantly higher insulin dose in the PRE group than Glargine group, but here no prandial insulin was added to Glargine.

4T trialinsulin doses were comparable between B-B and PRE groups.[15,19]

- In this study in B-B group there were 2 hypoglycemic episodes out of 25 and in PRE group no hypoglycemic episodes occurred. The p-value (0.149) is not significant.
- Raskin et al (Initiate study), demonstrated higher rates of hypoglycemia with PRE compared with Glargine. (No prandial insulin in Glargine in these studies). Durable study overall higher hypoglycemic events with PRE in comparison to Glargine (p-value=0.007).[16,19]
- Rosenstock J et al, Fritsche A et al, (GINGER study) B-B group had similar / even lower incidence of hypoglycemia in comparison to PRE.[13,15]
- Holman RR et al (4T trial) B-B regimen associated with fewer hypoglycemic events.[18]

CONCLUSION

In this observational cross sectional comparative hospital based study, the transition from i.v. insulin infusion to S.C. insulin, the Basal-Bolus regimen was compared with the conventional S.C. regimen.

The FBS in the B-B regimen achieved the target from the day of discharge till 2ndwk after discharge in comparison to the other two regimens and the change was statistically significant. The PPBS also achieved the target in the B-B regimen but statistically significant only after the 2ndwk after discharge compared only with PRE regimen.

The insulin dose (u/d) was high in NPH regimen compared to both B-B and PRE regimens and was statistically significant. There was no statistical significance in difference in insulin dose (u/d) between B-B and PRE regimens. The hypoglycemic events (60-70mg/dl) occurred in NPH and B-B, non in PRE, but NPH regimen was only statistically significant compared to B-B and B-B compared to PRE

ACKNOWLEDGEMENTS

Authors are extremely grateful to his teacher and guide Dr. Asutosh Ghosh for his continuous inspiration and guidance in my effort to undertake and complete this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Halder S, Biswas P, Sarkar D, Saha BK. Basal-bolus insulin therapy during switching over from continuous intra venous regular insulin to sub cutaneous insulin therapy as compared to conventional regimens in type-2 diabetes patients admitted in intensive care unit. Int J Res Med Sci 2016;4:4014-21.