Comparison of outcomes of different Insulin regimes in type 2 diabetics during peri-operative period: A randomised, single blind multi-centric study.

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Aims and Objectives: To compare the outcomes of different subcutaneous insulin regimes in type 2 diabetics during peri-operative period. Study design: This study is a multi-centric, prospective, single blind, randomised study. 289 type 2 diabetes mellitus patients undergoing major elective surgery 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. Subjects and Material: Each group received multiple injections from preoperative to postoperative period until the patients were switched back to the same treatment regime they received preoperatively. The starting dose of the insulin was 0.5 units per/kg body weight and then adjusted to maintain the average blood glucose level between 120-180 mg/dl during peri-operative period. The differences in mean daily blood glucose (BG) level and the incidence of complications attributable to postoperative outcome of specific treatment were recorded and compared. Chi-square test and ANOVA (one way classification) was employed for analysis of the data. A probability value of less than 0.05 (p<0.05) was considered to be statistically significant.

Results: Mean fasting blood glucose (BG) obtained a day before the treatment improved similarly in all the groups from a mean daily BG of 232.1±3.9, 229.0±3.6, 233.7±5.3 and 227.7±5.6 mg/dl to mean BG level after the first day of 146.4±0.7, 150.6±0.5, 143.2±0.9 and 140.3±0.7 mg/dl in regime A, B, C and D, respectively (p<0.001). The patients who received treatment regime A, C and D have shown significant difference (p<0.01, p<0.05, p<0.001) in incidence of hypoglycaemic episodes (BG <60 mg/dl), infection rate and mortality scores during peri-operative period. However, the least number of complications at low dose were recorded in patients who received treatment regime D (detemir+aspart). Conclusion: Treatment with basal/bolus regime of detemir once daily and aspart at comparatively low dose before meals resulted in minimum number of complications with less mean hospital stay during peri-operative period in type 2 diabetics.

Keywords: Insulin, type-2 diabetics, perioperative outcomes, NPH, lispro, aspart, glargine, detemir.

INTRODUCTION

Patients with diabetes mellitus (DM) undergo surgery at a higher rate than non-diabetics and are prone to adverse outcomes that can prolong hospital stay and increase mortality. (Umpierrez and Isaac 2002; Krinsley 2003). Surgery frequently disrupts the patient’s eating pattern, necessitating adjustments to the diabetes treatment regimen. Suboptimal glycaemia management during this time contributes to increased morbidity and aggravates the untoward effects of concomitant illnesses (Jesson 2003). Out of many diabetes associated complications, delayed wound healing and increased risk of infection are the major complications and leading cause of mortality in diabetic subjects (Zargar and Bashir 1999), (Bhansali and Chattopadhyay 2003). These complications of DM require special attention for all traumatic and infective
conditions including the modern surgery. To minimize the effects both of metabolic derangement on surgical complications and of the surgery on hyperglycaemia management in the peri-operative period depends on the ambient level of glycaemia control and the treatment regime (Marks 2003). Depending upon the type of diabetes, nature of surgery and timing of operation, many insulin and oral hypoglycaemic treatment regimes have been recommended for glycaemia control during peri-operative period (Amiel and Alberti 2002), (Hoogwerf 2001). The most frequent reason for endocrinology consultation in our hospital is uncontrolled blood glucose in type 2 DM patients admitted for different major surgical procedures. The control of peri-operative hyperglycaemia with subcutaneous insulin is a common practice in semi-urgent situation and even in case of planned surgery where there is oral drug failure in the stressful situation of disorders requiring surgery. Many subcutaneous insulin regimes are available but their superiority of glucose control in terms of surgical outcome during peri-operative period is not clear. Hence, in the present study four different subcutaneous insulin treatment regimes were observed for peri-operative outcome in type 2 DM patients undergoing major surgery.

Patients and Methods

Subjects: 289 type 2 diabetes mellitus patients that were admitted to surgical wards to undergo major surgery were enrolled. All the patients were referred to endocrinology unit of the concerned hospital participating in the study for metabolic management. The patients in whom the preoperative hyperglycaemia was to be controlled with subcutaneous insulin were studied. Old and newly diagnosed type 2 DM patients between 18-70 years of age were included and the patients on concomitant use of oral hypoglycemics, chronic corticosteroid or any other drug that either precipitates or aggravates the DM were excluded. The patients undergoing coronary artery bypass grafting surgery were also excluded. Written, informed consent of all the patients and approval of Institutional Ethics Committee (IEC) was obtained before starting the study. This study was conducted at Mahatma Gandhi Medical College and Hospital, S.M.S. Medical College & Hospital and Fortis Escorts Hospital, Jaipur, India.

Study design

This was a multi-centric, prospective, single blind randomised study. A total of 289 type 2 diabetes mellitus patients undergoing major elective surgery 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. A computer generated randomisation technique was attempted for treatment allocation to the groups and the insulin preparations were kept under the control of the trained ward nurse who was administering the respective insulin to the patients.

Study protocol

On enrolling the patients, routine investigation of fasting, random and post prandial blood glucose profile was done twice for confirmation. The history and duration of diabetes in addition to epidemiological characteristic profile was noted. After being educated on diet, importance of insulin with special emphasis on need to adhere to treatment, the patients were allocated to four treatment groups A, B, C and D receiving one of the four subcutaneous insulin regimes illustrated as;

A. Pre-mixed Regular: NPH in ratio 30:70
B. Split-mixed Regular+NPH
C. Split-mixed Glargine+Lispro
D. Split-mixed Detemir+Aspart

Each group was given multiple injections into the subcutaneous tissue of the upper arm, anterior and lateral aspects of the thigh, 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 they received preoperatively. The starting dose of the insulin was 0.5 units per kg body weight. Insulin dose was adjusted according to the pre- and post-meal blood glucose values. Any increase or decrease in insulin requirement was noted and compared with the goal to maintain the average blood glucose level between 120-180 mg/dl. In split-mixed regimes, regular insulin was given subcutaneously in three equally divided doses with each meal and long acting insulin was administered regardless of the patient’s oral intake status in the evening at bed time. Pre-mixed regime was given twice daily, before breakfast and before dinner.

Outcomes included differences in incidence of hypoglycaemic episodes, postoperative complications and mortality occurring among treatment groups.

Statistical analysis

Chi-square and ANOVA (one way classification) tests were employed for statistical analysis. The data was analysed with SPSS software (Version 10.0). A probability value of less than 0.05 (p<0.05) was considered to be statistically significant.

RESULTS

A total of 289 type 2 diabetes mellitus patients who completed the study were subjected to randomization for treatment allocation. 74 patients received premixed regular: NPH in the ratio of 30:70, 75 patients received
Table 1. Comparison of parameters in patients receiving different insulin regimes (among the group)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premixed Regular+NPH (n=74)</th>
<th>Split-mixed NPH+regular (n=75)</th>
<th>Split-mixed Glargine-lispro (n=69)</th>
<th>Split-mixed Detemir-aspart (n=71)</th>
<th>p- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose of insulin (units/day)</td>
<td>37.36 ± 0.82</td>
<td>36.24 ± 0.97</td>
<td>30.46 ± 1.44</td>
<td>31.50 ± 0.63</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Time to achieve glycemic target (hrs.)</td>
<td>8.17±0.46</td>
<td>6.81±0.38</td>
<td>5.73±0.18</td>
<td>6.7±0.10</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>16 (21.62%)</td>
<td>8 (10.66%)</td>
<td>9 (13.04%)</td>
<td>11 (15.9%)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Infection</td>
<td>10 (13.51%)</td>
<td>13 (22.80%)</td>
<td>8 (11.59%)</td>
<td>5 (7.04%)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>UTI</td>
<td>3 (4.5%)</td>
<td>10 (13.33%)</td>
<td>0 (0.00%)</td>
<td>3 (4.22%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>GIT</td>
<td>8 (10.81%)</td>
<td>7 (9.33%)</td>
<td>9 (13.04%)</td>
<td>0 (0.00%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>5 (6.75%)</td>
<td>3 (4.00%)</td>
<td>0 (0.00%)</td>
<td>1 (1.40%)</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

Figure 1. Comparison of complications of different insulin regimes: (among the groups).
A= Regular+NPH 30:70 (Premixed), B= Regular +NPH (Split-mixed), C= Glargine-lispro (Split-mixed), D= Detemir-aspart (Split-mixed), GIT= Gastrointestinal tract, WI= Wound infection, UTI= Urinary tract infection, *p<0.05, **p<0.01, ***p<0.001

split-mixed NPH+regular, 69 patients received split-mixed glargine+lispro and 71 patients received detemir+aspart insulin regimens respectively. All the treatment groups had more or less similar clinical and demographic characteristics. The most common admitting outcomes were hypoglycaemic episodes, postoperative complications and mortality scores among treatment groups.

The incidence of hypoglycaemic episodes recorded, were 21.6%, 10.6%, 13.0% and 15.1% in patients receiving treatment regime A, B, C and D respectively (Table 1; Figure 1). The least number of hypoglycaemic episodes were recorded in treatment regime B. But this difference was not statistically significant. Comparing the incidence of postoperative complications that occurred among treatment groups (Fig. 1), a significant difference came into view in gastrointestinal complications (p<0.001) and urinary tract infections (p<0.05). However, this difference in incidence of complications was not statistically significant for other complications recorded among groups. While comparing the complications within
Table 2. Comparison of parameters in patients receiving different insulin regimes (within the group)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premixed Regular+NPH (n=74)</th>
<th>Split-mixed NPH-regular (n=75)</th>
<th>Split-mixed Glargine+lispro (n=69)</th>
<th>Split-mixed Detemir+aspart (n=71)</th>
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<td>0 (0.00%)</td>
</tr>
<tr>
<td>p value</td>
<td>P&lt;0.01</td>
<td>p&gt;0.05</td>
<td>p&lt;0.05</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 2. Comparison of complications of different insulin regimes: within the group.
A= Regular+NPH 30:70 (Premixed), B= Regular+NPH (Split-mixed), C= Glargine+lispro (Split-mixed), D= Detemir+aspart (Split-mixed), GIT= Gastrointestinal tract, WI= Wound infection, UTI = Urinary tract infection, *p<0.05, ** p<0.01, ***p<0.001

Figure 3. Mortality rate according to regime
A= Regular+NPH 30:70 (Premixed), B= Regular+NPH (Split-mixed), C= Glargine+lispro (Split-mixed), D= Detemir+aspart (Split-mixed),
groups, a significant difference existed in treatment group A (p<0.01), C (p<0.05) and D (p<0.001) respectively (Table 2; Figure 2). In comparison to other regimes, the incidence of complications was significantly low in patients who received treatment regime D. The mortality rate was 6.7%, 4% and 1.4% in regime A, B, and D respectively (Table 1; Figure 3). No mortality was reported in patients who received treatment regime C. However, this difference was not statistically significant. The mean hospital stay of 8.1±0.4, 6.8±0.3, 5.7±0.1 and 6.7±0.1 days in patients treated with treatment regime A, B, C and D respectively was significantly different (p<0.001), the lowest being with glargine+lispro (i.e. in group C). The mean daily insulin dose to achieve the glycemic target was 37.3±0.8, 36.2±, 30.46±1.4 and 31.5±0.6 in regime A, B, C and D respectively (p<0.001).

**DISCUSSION**

Hyperglycemia is a common, serious, and costly health care problem associated with an increased risk of complications and mortality in critical and noncritical illness (Clement 2004, Finney 2003, Wahab 2002, Norhammar 1999, Montori 2002, Stranders 2004, Umpierrez 2004). Preoperative glycemic control has a significant impact on the risk of infections as complication including wound infection, urinary tract infection, and sepsis in patients with diabetes across a variety of surgical procedures (Dronge & Perkal 2006). Clinical studies have not consistently borne out the relationship between peri-operative glycemic control and short-term risk of infection or morbidity (MacKenzie 1988, Hjortrup 1985). Hypoglycaemia is an ever-present risk when the usual balance of calorie intake, activity, and medication is altered by the peri-operative fast and hormonal changes from surgery. This study has noted 21.6%, 10.6%, 13.0% and 15.9% hypoglycaemic episodes with premixed NPH/regular, split-mixed NPH/regular, glargine+lispro and detemir+aspart regimes respectively. The least number of hypoglycaemic episodes was noted in split-mixed NPH+regular regime. However, this difference in incidence of hypoglycaemic episodes among treatment regimes was not statistically significant (p>0.05) as depicted in Table 1. Our results are in accordance with a study stating no difference in frequency of hypoglycemic episodes between basal bolus regimes of detemir plus aspart and NPH plus regular in type 2 diabetes (Guillermo 2009). Another study has reported significantly lower incidence of hypoglycaemic incidences in those receiving glargine when compared to NPH (Methew 2003). A separate study reported no increased risk of hypoglycaemia in using premixed regime (Arnoff 1994). Infection is another major concern on which overall prognosis and cost of treatment depends. The present study noted that maximum number of patients who received split-mixed NPH/regular regime suffered from an infection. The results of this study are in accordance with a study that reported similar results (Mathur 2009). A study reported that the risk of post operative infection was significantly increased for patients with higher postoperative glucose levels (Golden 1999). The difference in incidence of urinary tract infection (UTI) among treatment regimes was statistically significant (p<0.05). No incidence of urinary tract infection (UTI) was recorded in patients who received glargine+lispro insulin regime.

Gastrointestinal complications were not seen in detemir+aspart regime while various GIT symptoms were recorded in patients who received other regimes. The difference in incidence of GIT complications among treatment groups was statistically significant (p<0.001). The mortality rate was more in patients who received premixed NPH/regular regime (6.7%). No case of mortality was reported in patients who received glargine+lispro regime. As against this 1.4% mortality was noted in patients who received detemir+aspart regime. However, this difference in mortality rate among different treatment regimes was not statistically significant (Table 1; Figure 3). While comparing the dose required in each group to treat, it was found that the average dose of insulin required to achieve the target was comparatively lower i.e. 30.4±1.4 units/day with glargine+lispro regime. This difference in insulin dose among regimes was statistically significant (p<0.001). The glargine+lispro group apparently showed early recovery as compared with other regimes. These results are supported by an earlier study reporting that glargine+lispro achieved the glycemic target in lesser time (Zerr 1997).

This study showed that number of complications was more in patients who received split-mixed NPH+regular regime in comparison to the patients who were treated with other treatment regimes (Fig 2). This could be due to higher blood glucose profile as reported by the study that a single blood glucose level greater than 220 mg/dl on the first postoperative day was a sensitive predictor of postoperative infection (Pomposelli 1998). Another study similarly reported that the infection in individuals with blood glucose between 207-209 mg/dl was increased by 17% (Golden 1999). In comparison to other treatment regimes, the detemir+aspart regime has shown significant difference (p<0.001) in reduction of complications at low dose with less mean hospital stay (Table 1; Figure 2). However, glargine+lispro has shown early recovery at lower dose with less number of complications in comparison to NPH regimes. This could be due to comparatively low postoperative blood glucose profile as is supported by a study reporting that maintaining the postoperative mean blood glucose levels less than 200 mg/dl reduces the incidence of infection in diabetic patients undergoing surgery (Zerr 1997).
CONCLUSION

The basal/bolus regimes of glargine+lispro and detemir+aspart are comparatively better in reducing the incidence of complications during surgery. However, least incidence of complications resulted in patients who received detemir+aspart insulin regime.

REFERENCES


