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A Comparison of Preprandial Mixed Insulin Given Three Times Daily and Basal-Bolus Insulin Therapy Started Postoperatively on Patients Having Coronary Artery Bypass Graft Surgery

Koroner Arter Bypass Cerrahisi Geçiren Hastalarda 3'lü Karışım ve 4'lü Yoğun İnsülin Tedavilerinin Karşılaştırılması

Dilek YAZICI[1], Serpil TAŞ[2], Hicran EMİR[3], Hasan SUNAR[2]

[1] *Sub-department of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Marmara University,İstanbul, Turkey*

[2] *Cardiac and Vascular Surgery Clinic, Kartal Koşuyolu Education and Research Hospital, İstanbul, Turkey*

[3] *Diabetes Education Nurse, Kartal Education and Research Hospital, İstanbul Turkey*

Abstract

Objective: Insulin therapy initiated after coronary artery bypass graft (CABG) surgery has decreased long-term mortality. The aim was to compare the effectiveness of prandial premixed therapy (PPT) using insulin thrice daily and basal-bolus therapy (BBT) on patients having CABG surgery.

Patients and Methods: Thirty-four patients having CABG surgery were included. Fasting blood glucose (FBG), postprandial blood glucose (PPBG), hemoglobin A1c (HbA1c) and hemoglobin levels were determined preoperatively and at the first week postoperatively when the patients were randomized to either PPT or BBT. Initial measurements were repeated at the end of three months.

Results: Seventeen patients (F/M:9/8; 61.5±8.5 years) were assigned on a random basis to the mixed insulin arm and 17 patients (F/M:10/7; 57.4±9.2 years) to the basal-bolus arm. FBG, PPBG and HbA1c levels of both groups (7.6±0.8 % vs 6.7±0.5 % in the BBT and 7.3±0.7 % vs 7.3±1.0 % in the PPT group) at the end of the 3 months were not different than at the time of randomization. The percentage of patients reaching HbA1c levels below 6.0%, 6.5% and 7.0% were higher in the BBT group compared to the PPT group.

Conclusion: For patients who had undergone CABG surgery, BBT provided more patients with HbA1c levels below the target than did PPT. *(Marmara Medical Journal 2012;25:16-9*

Key Words: Premeal mixed insulin therapy, Basal-bolus insulin therapy, Coronary artery bypass graft surgery

Özet

Amaç: Kalp cerrahisi sonrasında insülin tedavisi verilmesinin uzun dönemde mortalite üzerinde olumlu etkileri gösterilmiştir. Bu çalışmanın amacı kardiyak cerrahi geçirecek diyabetik hastalarda taburculuk sırasında düzenlenen 3'lü karışım insülin ve 4'lü bazal-bolus insülin tedavilerinin etkinliklerinin karşılaştırılmasıdır.

Hastalar ve Yöntem: Çalışmaya Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi'nde koroner arter bypass cerrahisi geçiren 34 diyabetik hasta dahil edilmiştir. Bu hastaların preoperatif dönemde açlık kan şekeri (AKŞ), tokluk kan şekeri (TKŞ), hemoglobin A1c (HbA1c) değerleri ve hemogramları belirlenmiştir. Postoperative1. haftada (taburculukta) aynı kan tetkikleri tekrarlanmış ve hastalara randomize olarak 3'lü veya 4'lü yoğun insülin tedavisi başlanmıştır. Üç aylık takip süresinin sonunda başlangıçta yapılan ölçümler tekrarlanmıştır.

Bulgular: Çalışmaya alınan 17 kişi (61,5±8,5 yıl; K/E:9/8) 3'lü kola (1. Grup), 17 kişi (57,4±9,2; K/E:10/7) ise 4'lü kola (2. Grup) randomize olmuştur. İki grupta da 3. ayın sonundaki AKŞ, TKŞ ve HbA1c değerleri (%7,6±0,8 ile %6,7±0,5 1. grupta ve %7,3±0,7 ile %7,3±1,0 2. grupta) randomizasyon sırasındaki değerlerden farklı değildir. Üçüncü ayın sonunda hedef %6,0, %6,5 ve %7,0 HbA1c değerlerine ulaşan hasta sayısı BBT grubunda PPT grubuna göre daha fazladır.

Sonuç: Koroner arter cerrahisi geçiren hastalarda BBT 3. ayın sonunda hedef HbA1c değerlerine ulaşan hasta yüzdesi açısından PPT tedavisinden daha etkilidir. *(Marmara Üniversitesi Tıp Fakültesi Dergisi 2012;25:16-9)*

Anahtar Kelimeler: Karışım insülin tedavisi, Bazal-bolus insülin tedavisi, Koroner arter bypass cerrahisi

Correspondence to/İletişim: Dilek Yazıcı, M.D., Sub-department of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Marmara University, Pendik, İstanbul 34988, Turkey
E-mail: dilekdy2002@yahoo.com

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Introduction

Hyperglycemia has been shown to be an independent predictor of perioperative morbidity and mortality both in diabetic and non-diabetic patients. Preoperative high HbA1c levels have been related to increased risk of perioperative myocardial infarction[1]. Insulin therapy initiated after cardiac surgery has decreased long term mortality[2]. Good glycemic control in patients having coronary artery bypass graft (CABG) surgery has increased survival and decreased ischemic events and surgical wound infection postoperatively[3,4].

Insulin infusion therapy is the accepted modality of therapy at the perioperative period and in the intensive care unit (ICU) following surgery. However, there is also data implicating that intravenous insulin sliding scale may not provide effective glucose control postoperatively[5]. At the time of clinical stabilization, either in the ICU or at discharge to the ward, intensive subcutaneous insulin therapy is recommended[6]. Basal-bolus therapy (BBT) is the usual recommended regimen for insulin intensification[7]. Prandial premixed therapy (PPT) is another option of intensification of insulin therapy. It may be a more convenient regimen, and has the potential to be as effective as BBT[8-11]. The head-to-head comparison of analog BBT and three times daily PPT has failed to show noninferiority of PPT in type 2 diabetic patients treated previously with insulin glargine plus oral agents[12].

The aim of our study was to compare the efficiacy of BBT and PPT three times daily initiated in patients having CABG surgery at a follow-up period of 3 months.

Patients and Methods

Patients were consequetively selected among diabetic patients hospitalized for coronary artey bypass graft (CABG) surgery. A medical history was obtained from all patients and controls, followed by a physical examination. The duration of diabetes and the presence of complications were noted. Blood was withdrawn preoperatively for determination of fasting blood glucose (FBG), post-prandial blood glucose (PPBG), hemoglobin A1c and hemoglobin. Inclusion criteria were type 2 diabetic patients who were on oral anti-diabetic therapy. Exclusion criteria were patients who were already on insulin therapy, patients with chronic renal failure, congestive heart failure with New York Heart Association (NYHA) classification of class III, IV, any other chronic disease and patients taking steroids. The patients were on intensive insulin therapy before the operation. Insulin infusions were given perioperatively and at the ICU following CABG. Then patients were consequetively assigned to either BBT with insulin glargine and lispro or to PPT with insulin lispro-lispro protamine mix 50 combination, three times daily. This was done one week after the surgery, which is the usual time of discharge from the hospital. Blood was then withdrawn to determine FBG, PPBG, HbA1c and hemoglobin. In the BBT group, 50% of the insulin requirements of the patients were given as bolus therapy and the other 50% were divided equally three times daily as the bolus therapy. In the PPT group, the total insulin requirements were divided equally at each main meal. The patients were followed by the results of capillary 6 point FBG and PPBG measurements taken at home (6 point meaning a FBG before and a PPBG two hours after breakfast, a FBG before and a PPBG two hours after lunch and a FBG before and a PPBG two hours after dinner). Insulin doses were adjusted by the same physician according to these measurements every 15 days. The follow-up period was 3 months and FBG, PPBG, HbA1c and hemoglobin levels were determined at the end of the 3 month interval. The study protocol was approved by the local research ethics committee and was carried out in accordance with the declaration of Helsinki. All subjects gave written informed consent.

FBG and PPBG levels were determined by the enzymatic calorimetry method. HbA1c was determined by the high-performance liquid chromatography (HPLC) method.

Statistical Analysis

The statistical analysis was performed with a SPSS 15.0 software package. Comparisons of continous variables were done using Student's unpaired t test or Wann-Whitney U test according to the distribution of values. The Chi-square test was used for the comparison of categorical variables. The changes in FBG, PPBG and HbA1c levels between the preoperative period and the first week and the first week and postoperative 3 months were evaluated by paired t test. Levels of statistical significance were set at a p value <0.05. The results were expressed as mean±SD.

Table I. Demographic and biochemical characteristics of the study groups

	PPT ARM (n:17)	BBT ARM (n:17)	p
Sex (F/M)	9/8	10/7	NS
Age (years)	61.5±8.5	57.4±9.2	NS
Disease duration (years)	11.7±9.7	5.6±5.0	0.01
Systolic BP (mmHg)	122±12	118±11	NS
Diastolic BP (mmHg)	76±8	75±7	NS
FBG (mg/dL)	231±90	251±75	NS
PPBG (mg/dL)	213±86	208±12	NS
HbA1C (%)	8.1±1.2	9.7±1.8	NS
Hb	12.5±1.8	12.8±1.4	NS

*Values are expressed as means ± SD or means ± SEM according to the distribution of variables. PPT= preprandial mixed insulin therapy, BBT= basal-bolus insulin therapy, F/M=Female/Male, NS=not significant, BP=blood pressure, BMI=body mass index, WHR=waist-hip-ratio, FBG=fasting blood glucose, PPBG=postprandial blood glucose, Hb= hemoglobin

Results

Seventeen patients (F/M:9/8; 61.5±8.5 years) were randomized to the PPT arm and 17 patients (F/M:10/7; 57.4±9.2 years) were randomized to the BBT arm. The ages and F/M ratios of both groups were comparable. The duration of diabetes in the basal-bolus group was longer than in the mixed insulin group (11.7±9.7 years vs 5.6±5.0 years) (Table I). The first-week FBG levels and the levels at randomization, were lower than the preoperative levels in both groups (146.6±64.5mg/dL vs 250.7±75.4mg/dL, p=0.005 in the BBT group and 125.9±47.9mg/dL vs 230.9±90.6mg/dL,

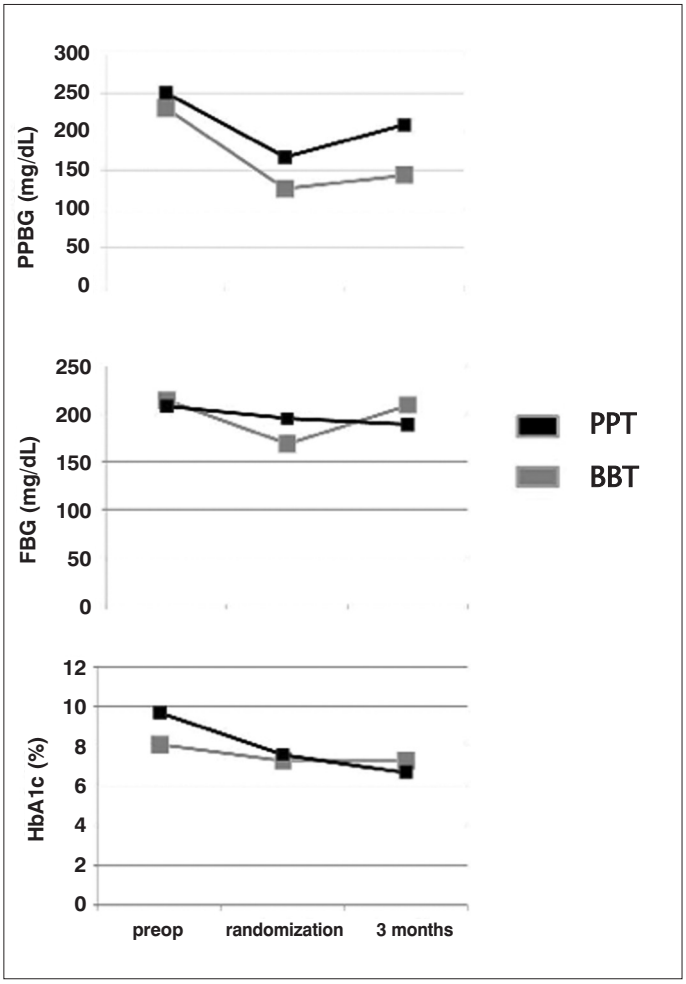

Figure 1. The change in FBG (upper graph), PPBG (middle graph) and HbA1c (lower graph) at baseline, at randomization and month 3.

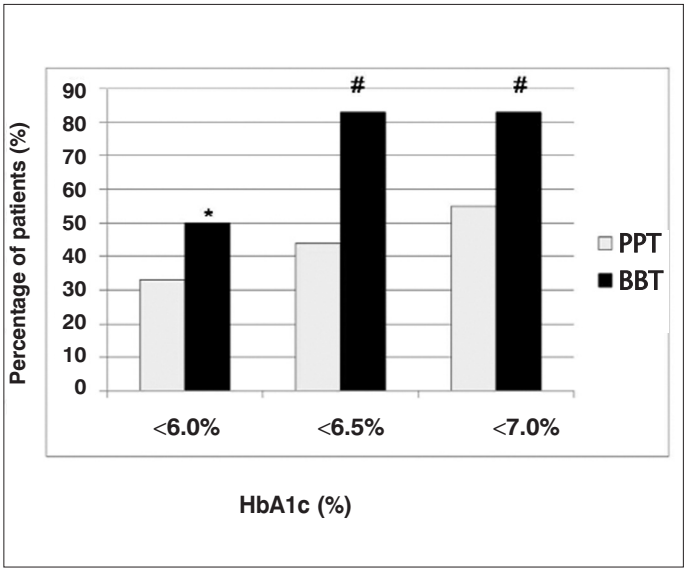

Figure 2. The percentage of patients reaching a target HbA1c of below 6.0%, 6.5% and 7.0%. The percentage of patients reaching a target HbA1c of below 6.0% were higher in the BBT group with *p=0.002. The percentage of patients reaching a target HbA1c of below 6.5% and 7.0% were higher in the BBT group with # p<0.000.

p=0.004 in the PPT group). There was no difference in terms of the PPBG levels at the time of randomization compared to the preoperative levels (194.8±55.3 mg/dL vs 208.0±12.1mg/dL in the BBT group and 167.8±36.5mg/dL vs 213.8±26.2mg/dL in the PPT group). The HbA1c in the BBT group was significantly lower at the time of randomization compared to the preoperative levels (7.6±0.8% vs 9.7±1.8%,p=0.04). Although the HbA1c levels in the PPT group were also decreased at the time of randomization compared to the preoperative levels, the decrease was not significant (7.6±0.8% vs 9.7±1.8%). The FBG (125.5±16.4mg/dL in the BBT and 143.8±37.4 mg/dL in the PPT group), PPBG (189.2±40.0mg/dL in the BBT and 208.5 ± 80.4 mg/dL in the PPT group) and HbA1c levels (6.7±0.5% in the BBT and 7.3±1.0% in the PPT group) of both groups at the end of the 3 months follow-up period were not different than at the time of randomization, although there was a tendency for the HbA1c in BBT group to be lower (Figure 1). Hemoglobin levels were not different at any of the time points (data not shown).

The data were evaluated as the percentage of patients reaching target HbA1c levels in both groups. There was an increase in the percentage of patients with HbA1c<6.0 in the PPT group at the end of 3 months in comparison to the postoperative 1st week. However, no difference was evident in patients with HbA1c <6.5% and <7.0%. In the BBT group, the percentage of patients having HbA1c below 6.0%, 6.5% and 7.0% were all increased at the end of 3 months in comparison to the postoperative 1st week. Concerning the levels at the end of 3 months, the percentage of patients reaching HbA1c levels below 6.0%, 6.5% and 7.0% were higher in the BBT group compared to the PPT group (Figure 2).

Discussion

The study showed that the insulin therapy initiated at discharge as BBT or PPT in patients having CABG surgery did not cause any significant change in FBG, PPBG and HbA1c levels at the end of follow-up of three months. On the other hand, significant increases were observed in the number of patients reaching target HbA1c levels in both groups, only in <6.0 in the PPT and for all values of <6.0%, 6.5% and <7.0% in the BBT group. When the 3 month endpoint values are concerned, BBT seeems to be more effective in providing higher number of patients reaching all target HbA1c levels. When we look at the data closely, we find out that there was a tendency for the HbA1c levels to be decreased in the BBT group, but the difference did not reach statistical significance. This was strenghtened by the higher number of patients having HbA1c below <6.0%, 6.5% and <7.0%. in this group. This finding is compatible with the previous findings by Rosenstock et al, who also did a head-to-head comparison of 187 patients randomized to BBT and 187 patients randomized to PPT, in patients that were inadequately controlled with basal glargine therapy plus oral antidiabetic agents[12]. They observed an HbA1c decline of 2.09% in the BBT group and a decline of 1.87% in the PPT group. A higher percentage of patients in the BBT group reached HbA1c targets of <6.5% and 7.0% compared to the PPT group. FBG and PPBG levels were decreased at all the 8 point measuring times, the values of fasting and morning 2-hr PPBG being lower in the BBT group[12].

Our findings of a higher number of patients reaching target HbA1c levels are compatible with Rosenstock's findings. However, no significant decline of HbA1c, FBG or PPBG was evident in either group. This may be explained by the fact that a significant improvement of HbA1c and decrease in FBG and PPBG levels was evident at the time of randomization, compared to the preoperative HbA1c, FBG and PPBG levels. This is due to the vigorous control of diabetes with insulin infusion at the ICU and intensive insulin treatment at the ward. Moreover, the patients were on a strict diabetic diet. The fact that FBG and PPBG levels were decreased is evident due to the insulin given. Moreover, the significantly decreased HbA1c levels cannot be explained by the blood loss during surgery, since we determined hemoglobin levels before and after surgery and found them to be stable. Thus the decline in HbA1c seems to be a direct result of the strict glucose control perioperatively. On the other hand, the transfusions from nondiabetic people given during the operations might have affected the percentage of glycosylated hemoglobin in these patients. The FBG, PPBG and HbA1c levels were close to normal levels at the time of randomization. However, significant increases were observed in reaching target levels in both groups, but only for the <6.0 target in the PPT group and for all values of the target <6.0%, 6.5% and <7.0%. in the BBT group.

This is the second head-to head comparison of PPT and BBT. There have been other studies of PPT. Jacober et al compared the efficacy of PPT and basal glargine therapy in poorly controlled type 2 diabetic patients and determined that PPT was more effective in decreasing HbA1c and PPBG levels[9]. Similar results were reported by a similarly designed study by Robbins et al. [11]. In another study, prandial lispro therapy and lispro-lispro protamine mix therapy three times daily achieved lower HbA1c due to lowered PPBG levels[10].

Although statistically not significant, HbA1c levels in the BBT group at the time of randomization was higher than the PPT group. This might have affected the response rate in the BBT group since it is more probable to achieve higher amount of decrease of HbA1c levels compared to lower ones. Moreover, the patients in the BBT group were younger and their disease duration was lower than the patients in the PPT group. These are other factors that are in favor of the HbA1c decrease rate in the BBT group. Thus performing the comparisons of BBT and PPT in a more homogenous population may correct for these confounding factors.

The major limitation of the study is the low number of patients in the study groups. Besides, the fact that the groups were not matched for age and disease duration are the other drawbacks of the study as mentioned above.

In conclusion, both BBT and PPT were able to increase the number of patients having HbA1c levels below 6.0%. BBT was more effective in increasing the number of patients having an HbA1c of below <6.0%, 6.5% and <7.0% at the end of a follow-up of 3 months. Moreover, BBT was more effective in increasing the percentage of patients below the final target HbA1c levels of <6.0%, 6.5% and <7.0%. in comparison to the PPT. Larger populations with a longer period of follow-up may give more information about which intensive insulin therapy to apply in post-CABG surgery patients.

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