Original Article

Blood Glucose Control and Opportunities for Clinical Pharmacists in Infectious Diseases Ward

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ABSTRACT

Objective: Increased risk of infection following hyperglycemia has been reported in hospitalized patients. Sliding-scale insulin protocol is an out-of-date method; therefore, it is necessary to examine new approaches in this regard. This study aimed to evaluate the efficacy of sliding-scale protocol versus basal-bolus insulin protocol, which supervised by clinical pharmacists in an infectious disease ward. **Methods:** In this prospective randomized clinical trial, 90 hyperglycemic patients who hospitalized in Loghman Hakim Hospital Infectious Disease Ward (Tehran, Iran) were randomized into two groups: sliding-scale insulin protocol (the control group) and the basal-bolus protocol groups that were under supervision clinical pharmacists. Some demographic, laboratory, and clinical variables, as well as patient's blood glucose were measured four times daily. **Findings:** The results indicated significant improvement among the patients in the intervention group. General indicators including fever, blood glucose level, the duration of hospitalization, incidence of hypoglycemia, days to achieve normal blood glucose, and leukocyte count improved in intervention group. **Conclusion:** According to this study, basal-bolus insulin protocol, which supervised by clinical pharmacy service, showed better blood glucose control and infection remission compared to the sliding-scale protocol.

KEYWORDS: *Cellulitis, diabetes mellitus, hyperglycemia, pharmacy service, pneumonia*

INTRODUCTION

Diabetes mellitus is a significant cause of morbidity and mortality, which needs careful monitoring and control from diagnosis.[1] Blood glucose level monitoring is one of the most important medical challenges, especially in the infectious diseases ward.[2] High blood glucose level suppresses the immunity system. Hence, the risk of secondary infections can increase. This effect is more critical in patients with underlying infectious diseases or those that are undergoing surgical operations.[3] Hence, effective blood glucose controlling is a crucial mission in an infectious disease ward. There are several strategies to control the blood glucose of patients who have been admitted to the hospital. The most common approach to treat hospitalized patients with diabetes mellitus is sliding-scale insulin therapy. In the sliding-scale method, premeal insulin dose adjusted based on the blood glucose level before the meal.[4] Although sliding-scale insulin therapy is an inefficient and out-of-date method, as reported by several previous studies. However, it remains as the most used method due to its feasibility.[5] This method is unable to decrease highly elevated glucose levels and may worsen the situation through hypoglycemia. This method does not consider the patient's diet, weight, previous insulin dose, and patient's sensitivity to insulin. Due to the problems mentioned above, most guidelines discouraged using sliding-scale insulin therapy.[6] Hence, it is necessary to employ other strategies, such as bolus fixed doses of basal insulin. Some studies mentioned the critical role of clinical pharmacists in infectious diseases

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ward by effective blood glucose control.[7,8] Hence, the implementation of a clinical pharmacist can help to better blood glucose control. This study aimed to evaluate the efficacy of sliding-scale protocol versus basal-bolus insulin protocol, which supervised by clinical pharmacists in an infectious diseases ward of a University Hospital in Tehran, Iran.

Methods

This study was a randomized clinical trial which conducted in Loghman Hakim Teaching Hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the protocol of this study with number IR.SBMU.PHNM.1395.606, and this trial registered in the Iranian Registry of Clinical Trials with number IRCT20130917014693N9. This study was done between April 2017 and September 2017. The sample size of this study was estimated by GPower software (Heinrich Heine Universität Düsseldorf, Germany). It showed a sample size of 90 would have >80% power to detect a statistically significant change by effect size = 0.6 by alpha = 0.05 (two-tailed). Ninety patients who hospitalized in the infectious diseases ward were enrolled in this study. Inclusion criteria of this study were as follow: (1) patients who hospitalized in infectious diseases ward due to three important infections which diagnosed by infectious diseases specialist (pneumonia, cellulitis, and diabetic foot infection); (2) had diabetes mellitus as comorbidity which diagnosed by endocrinologist specialist; (3) were more than 18 years old; and (4) were on subcutaneous insulin regimen. Patients with following criteria were excluded from the study: (1) pregnant patients; (2) surgical patients; (3) patients with end-stage renal disease (glomerular filtration rate <10 mL/min); (4) patients on intravenous insulin; (5) patients on total parental nutrition; and (6) patients who did not sign the patient informed consent form. The included patients randomized into two equal groups (n = 45) as control and intervention groups. The randomization was done through computer software (Sealed Envelope Ltd., London, UK). Patients in the control group received the sliding-scale insulin therapy. According to this protocol, a varying dose of regular insulin administered based on the blood glucose level before the meal (measured every 6 h). In the intervention group, the needed daily insulin dose for each patient calculated and then converted to one dose of long-acting insulin (neutral protamine Hagedorn + regular). These doses were given in the morning and evening. In both groups, none of the oral antidiabetic agents administered. Patients received basal-bolus insulin based on the American Diabetes Association (ADA) guideline, and this intervention was done under the supervision of a clinical pharmacist.[9]

Then, the patients were visited daily by a physician and a clinical pharmacist. Demographic variables, laboratory variables, and clinical variables including age, sex, weight, type of infection, glycosylated hemoglobin (HbA1c), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, white blood cell count (WBC), hemoglobin, serum creatinine, fever grade, level of consciousness, and nutritional status were measured. Furthermore, the blood glucose level was measured every 6 h. Specific indicators for each infection were recorded. The severity of pneumonia was evaluated by heart rate, blood pressure, respiratory rate, oxygen saturation, and CURB-65 pneumonia severity score (confusion, blood urea > 42,8 mg/dl, respiratory rate > 30/min, blood pressure < 90/60 mm Hg, age > 65 years). The severity of diabetic foot infections was determined by perfusion, extent, depth, infection, and sensation. The wound area among both diabetic foot infection and cellulitis patients were monitored daily by the wound mapping factor. Parameters related to the control of underlying infectious diseases such as fever, duration of hospitalization, and rate of mortality were also recorded. All variables measured at baseline and the end of the study. Data were analyzed using the Statistical Package for the Social Sciences, SPSS software (IBM Corp., Released 2013. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA: IBM Corp.). The statistical tests employed for data analysis were Independent t-test, Chi-square test, or Fisher's exact test where appropriate. $P < 0.05$ considered as statistically significant level.

Results

A total of 90 patients with each of community-acquired pneumonia, cellulitis, or diabetic foot infections were evaluated between April 2017 and September 2017. The Consolidated Standards of Reporting Trials diagram of the current study is shown in Figure 1. Evaluation of baseline parameters (age, sex, HbA1c, serum level of creatinine, hemoglobin, platelet count, ESR, CRP, level of consciousness, fever grade, WBC, and nutritional status) demonstrated no significant difference between two groups. Evaluation of outcomes related to controlling blood glucose level revealed a statistically significant between the two groups. In the intervention group, all blood glucose levels were in the accepted range [Table 1]. Evaluation of outcomes related to the time needed to achieve normal blood glucose levels also demonstrated that this time was shorter in the intervention group [Table 2].

The results of secondary outcomes evaluation are shown in Table 3. All secondary outcomes were improved in the intervention group.

Among pneumonia patients, oxygenation lasted 10.15 ± 5.01 days to improve for control and 5.64 ± 1.69 days to improve for the intervention group (P = 0.01). Tachypnea lasted 9.17 ± 4.83 days for the control group and 5.44 ± 2.01 days for the intervention group to resolve (P = 0.06). The secondary outcomes among diabetic foot infection patients are shown in Table 4.

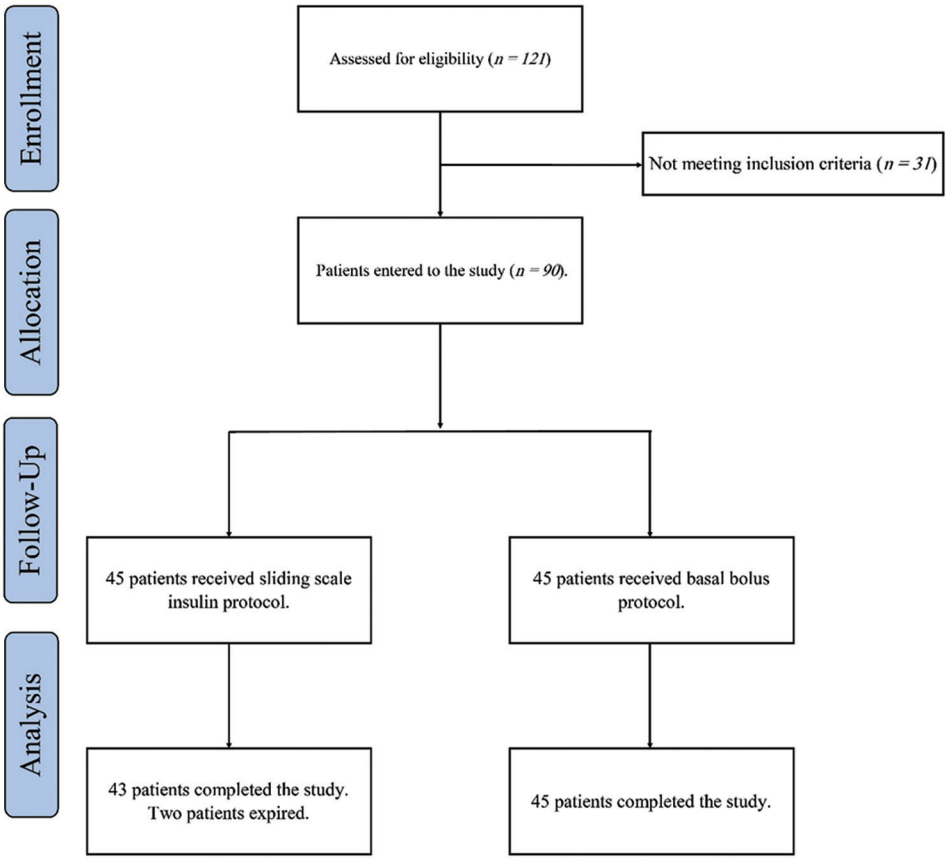

Figure 1: The Consolidated Standards of Reporting Trials (CONSORT) diagram of the current study

Table 1: Results of blood glucose measurement in the studied patients

Parameter	Disease	Control	Intervention	*P*
Percentage of patients with normal FBS	CAP	64% (9)	85% (12)	0.079
	DFI	33% (5)	80% (12)	0.01*
	Cellulitis	66% (10)	86% (13)	0.195
Percentage of patients with normal BS	CAP	43% (7)	71% (10)	0.127
	DFI	26% (4)	66% (10)	0.028*
	Cellulitis	53% (8)	73% (11)	0.256
Percentage of patients with normal total daily blood glucose	CAP	25% (4)	57% (8)	0.025*
	DFI	6% (1)	40% (6)	0.014*
	Cellulitis	20% (3)	46% (7)	0.029*
Percentage of patients with hypoglycemia	CAP	62% (10)	35% (5)	0.011*
	DFI	26% (4)	20% (3)	0.006*
	Cellulitis	46% (7)	20% (3)	0.051
Percentage of patients with normal blood glucose during all days	CAP	34.29%±22.14%	42.13%±21.81%	0.001*
	DFI	20.33%±17.40%	34.60%±18.42%	0.34
	Cellulitis	24.53%±24.85%	36.67%±17.94%	0.004*

*Significant result (P≤0.05). CAP=Community-acquired pneumonia, DFI=Diabetic foot infection, FBS=Fasting Blood sugar, BS=Blood sugar

Table 2: Time to achieve normal blood glucose in studied patients

Parameter	Disease group	Control	Intervention	*P*
Time to achieve normal FBS (day)	CAP	7.11±5.28	2.17±1.47	0.01*
	DFI	6.80±2.39	5.33±2.46	0.28
	Cellulitis	4.50±2.17	3.08±1.55	0.08
Time to achieve normal daily blood glucose (day)	CAP	8.33±6.81	2.00±0.76	0.02*
	DFI	8.50±0.71	6.00±1.79	0.11
	Cellulitis	6.00±3.61	3.57±2.57	0.025*

*Significant result ($P \leq 0.05$). CAP=Community-acquired pneumonia, DFI=Diabetic foot infection, FBS=Fasting blood sugar

Table 3: Results of secondary outcomes evaluation among all subjects

Parameter	Control	Intervention	*P*
Duration of hospitalization (day)	10.39±4.39	9.98±4.26	0.65
Time to fever resolution (day)	6.42±3.36	5.3±3.48	0.23
Time to achieve normal WBC (day)	7.16±3.78	6.61±4.29	0.64
Mortality	4% (2)	0% (0)	0.001*

*Significant result ($P \leq 0.05$). WBC=White blood cell

Table 4: Results related to diabetic foot infection secondary outcomes

Parameter	Control	Intervention	*P*
Secretion reduction (%)	52.66%±17.91%	70.71%±15.42%	0.007*
Wound mapping reduction (%)	46.14%±16.72%	70.33%±17.16%	0.046*
Debridement (*n*)	2.00±1.37	0.79±0.63	0.001*

*Significant result ($P \leq 0.05$)

Among cellulitis patients, wound mapping significantly improved in the intervention group. 44.00% ± 12.42% wound mapping reduction in control group and 55.33% ± 15.97% in intervention group ($P = 0.039$).

Discussion

The aim of this study was to evaluate the efficacy of sliding-scale protocol versus basal-bolus insulin protocol, which supervised by clinical pharmacists in the infectious diseases ward. The standards of this study and also the overall methods and instructions are based on ADA guidelines 2015.[9] As mentioned, blood glucose and infections have a reciprocal relationship as the worsening of one may worsen the other.[10] Since 2009, the ADA guideline has suggested insulin therapy for the critically patients with hyperglycemia or blood plasma glucose above 180 mg/dl. ADA and American Association of Clinical Endocrinologists guidelines also suggested the normal level for blood glucose as 140–180 mg/dl.[11]

The results of the current study generally demonstrate that better control on blood glucose levels was seen among the basal-bolus insulin group. In each group, infection resolution improved along with better glucose control. However, results related to the percentage of patients with normal blood glucose and diabetic foot infection did not show a statistically significant improvement compared to the control group. This pattern was probably due to the severity of the disease and higher levels of HbA1c at the baseline. Brenner demonstrated that intensive blood glucose control in diabetic patients is essential to improve diabetic foot infection.[12] Kitabchi and Nyenwe proved the beneficial effect of discontinuing sliding-scale insulin protocol in various hospital wards. However, more studies are needed to support this claim.[13] Similar the current study design, Umpierrez *et al.* evaluated the efficacy of sliding-scale insulin therapy versus basal-bolus insulin. In that study, one group received a sliding-scale insulin protocol and the other one received a basal-bolus insulin protocol. This study leads to better blood glucose control among the basal-bolus insulin group, which confirms the current study. The main limitation of that study was the lack of accurate randomization and heterogeneous baseline parameters.[14]

Another prospective study in 2014 by Zaman Huri *et al*. concluded there are lower levels of fasting blood glucose and lower average daily glucose level among the basal-bolus insulin group.[15] Similar results were observed in the current study, which showed more normal glucose levels among the intervention group compared to the control group. In the current study, hypoglycemia incidence in the intervention group was 25%, which is notably decreased compared to the control group (45%). Therefore, a basal-bolus protocol is highly capable of decreasing hypoglycemia incidence among inpatients. Arinzon *et al*. and Jan *et al*. in 2009 proved that hypoglycemia may happen as a reason for underlying infection and effectively increases the mortality rate.[16,17] The results show that the average hospitalization period decreased although not significantly, probably due to the limited course of the study. The average hospitalization period in the infectious diseases ward is 4–10 days, which is relatively short. Therefore, a long-term evaluation of the effect of blood glucose controlling on hospitalization duration was not possible. Van den Berghe *et al*. studied 1200 ICU patients in 2006 and demonstrated that basal-bolus can decreases (3 days) hospitalization period, compared with sliding-scale protocol.[18,19] Fever resolution was observed 2 days earlier for the intervention group compared to the control group, although not significantly due to a limited course of study and a short period of hospitalization. Leukocytosis diminished 1 day earlier for the intervention group compared to the control

group, although not to a significant degree due to various causes such as differences in disease severity, limited course of hospitalization, and the incompetency of the protocol for controlling WBC count. Previous studies showed that intensive blood glucose control helps decreases the fluctuations in the activity of the immune system and regulates the release of inflammatory mediators.[20] This study shows the effect of controlled blood glucose on mortality reduction. However, since the sample size is comparably small, more investigations are recommended. Marston *et al*. demonstrated that better control of blood glucose results in significant infection remission among patients. This effect was also observed through the current study.[21] Among diabetic foot infection patients, evaluation of wound mapping and wound secretions is crucial to estimate wound healing. Both mentioned parameters decreased significantly among the intervention group with $P = 0.046$ for wound mapping reduction and $P = 0.007$ for wound secretion reduction. The average wound debridement in the intervention group was 0.79, whereas it was 2.00 for the control group, showing a sensible reduction in the intervention group. These observations also demonstrate the efficacy of our protocol on the patient's clinical condition. Among infectious cellulitis patients, the average reduction in wound mapping was higher significantly in the intervention group. On the period of oxygenation among pneumonia patients, it lasted up to 10 days for the control group, whereas only 5 days for the intervention group. Castellanos *et al*. studied in 2012 on elderly diabetic patients with pneumonia, revealed that even a slight elevation in average daily blood glucose, especially fasting blood glucose between 101 and 125 mg/dL is capable of increasing pneumonia complications.[22] A similar study also conducted by a team of clinical pharmacists on the role of clinical pharmacists in educating patients about the proper method of insulin injection and the importance of blood glucose control, especially in the course of infection treatment.[7] This study had some limitations, such as lack of randomization and control group. Both mentioned limitations have been resolved in the current study. Notably, the prominent finding of this study was the significant effect of blood glucose control on infection improvement. A multidisciplinary team, including a clinical pharmacist, may significantly affect the course of treatment to reduce mortality and morbidity and improve the quality of life in diabetic patients. A notable finding through the course of study was the impressive role of the clinical pharmacist as a member of health-care providers to provide blood glucose control protocol as an effective tool to achieve various improvements in the course of treatment.

Authors' Contribution

Minoosh Shabani and Zahra Sahraei proposed the idea and supervised the whole project. Maryam Rashedi and Sareh Razzazzadeh involved in the clinical aspects and data gathering. Ali Saffaei analyzed the data and commented on the presentation of the results. All authors involved in the manuscript preparation and finally all of them revised and approved the final version of manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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