Research Article

Comparison of Insulin Protocols in Critically ill Patients

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1. Abstract

1.1. Background and Aim: This study aimed to determine the best protocol in the treatment of stress-related hyperglycemia and insulin resistance.

1.2. Materials and Methods: A total of 30 patients under mechanical ventilation were included in the study. We investigated the effect of intensive insulin treatment on mortality and morbidity by performing three different insulin protocols and close glycemic control. We compared blood glucose levels, blood lipid profiles, ventilator-related pneumonia development, C-reactive protein levels and blood lactate levels between protocols.

1.3. Results: The statistical comparison of the groups showed no difference regarding the mean age of the patients ($p>0.05$), APACHE II scores observed 24 hours after admission to the intensive care unit ($p>0.05$), and the blood glucose levels before intervention ($p>0.05$). As for the insulin infusion doses administrated within the 15-day follow-up period, there was no difference among groups ($p=0.7752$). The number of hypo- ($<60\,mg/dl$) and hyperglycemic ($>117\,mg/dl$) events observed in the Leuven, CUP and Graz protocols were statistically compared, and no significant difference was observed ($p>0.05$).

1.4. Conclusion: All three protocols analyzed in this study may be used for glycemic control and these protocols are similarly effective in reducing CRP values, regulating blood lipid profiles and reducing the development of ventilator-related pneumonia.

3. Introduction

Many studies have demonstrated that intensive care unit (ICU) mortality may be reduced by the hypergycemic control and keeping blood glucose level below 110 mg/dl. The ability of this protocol to simply intervene through glycemic control, which reduces mortality rates significantly, suggests that every ICU must implement an insulin protocol.

4. Material and Methods

4.1. Study Design: This study was approved by the local Institutional Review Board. Written informed consent was obtained from all subjects, a legal surrogate or legal guardians. A total of 30 patients on mechanical ventilation in ICUs were included in the study. The participants were randomly divided into three insulin protocol groups. Insulin was administered according to the Leuven Protocol (LP) in Group I, Charles University Protocol (CUP) in Group II and Graz Protocol (GP) in Group III. Those who were hospitalized in the ICU due to septic shock, diabetic coma or intoxication, pregnants or those allergic to insulin were excluded from the study.

4.2. Outcome Parameters: Administrated insulin protocols were described as follows. Leuven Protocol in Appendix 1, Charles University Protocol in Appendix 2, and Graz Protocol in Appendix 3. Baseline blood glucose level on admission was recorded for each patient and one of the three insulin protocols were started in a randomized manner. Blood glucose measurements were performed with arterial blood samples using a whole-blood analyzer (ABL 700, Radiometer, Copenhagen, Denmark). APACHEIIscores were checked 24 hours after admission. Potassium and blood lactate levels and leukocyte counts were checked daily. Endotracheal tube cultures were obtained, C-reactive protein (CRP), triglyceride, cholesterol, HDL and LDL levels were checked two times a week and body temperature at every hour. Blood culture was performed when body temperature was over 38°C. The diagnosis of ventilator-related pneumonia (VRP) was made upon fever concomitant with bacterial growth in tracheal

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culture, leukocytosis or leukopenia, increase in CRP and presence of infiltration in direct microscopy. Development of either hypo- or hyperglycemia was recorded.

4.3. Statistical Analysis: Data were analyzed using the Statistical Package for Social Sciences 10.0 for Windows (SPSS Inc., Chicago, IL). Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Comparisons were made using 'ANOVA and Tukey HSD, Kruskal Wallis' test. Variance analysis and chi-square test were used for repetitive measurements. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

5. Results

A total of 30 patients met the eligibility criteria for the study. Of the 30 patients (15 males, 15 females) whose charts were reviewed, the mean age was 53.0±20.0 (range 18 to 80) years. The statistical comparison of the groups showed no difference regarding the mean age of the patients (p>0.05), APACHE II scores observed 24 hours after admission to the ICU (p>0.05), and the blood glucose levels before intervention (p>0.05).

As for the insulin infusion doses administrated within the 15-day follow-up period, there was no difference among groups (p=0.7752) (**Table 1**). Insulin doses were 432.30±641.75 IU for Group I (Leuven), 489.90±475.08 IU for Group II (CUP), and 328.70±361.07 IU for Group III (Graz).

There was no statistically significant difference between groups regarding 4-week follow-up of leukocyte count (p>0.05). The leukocyte count in the 2nd, 3rd and 4th weeks were significantly lower in Group I than the 1st week (p<0.05 p<0.01). In Group II, the 2nd, 3rd and 4th week leukocyte count values were significantly reduced compared to the 1st week (p<0.01). In Group III, no significant difference was observed in leukocyte count (p<0.05) (**Figure 1**).

No statistically significant difference was observed among groups regarding the CRP values on the 2nd, 3rd and 4th weeks (p>0.05). The comparison of CRP values according to week revealed no significant difference in any of the groups (**Figure 2**).

No statistically significant difference was observed between groups regarding triglyceride values (p>0.05) (**Figure 3**), lactate values on admission or on the 2nd or 3rd weeks (p>0.05) (**Figure 4**) and the development of VRP (p>0.05).

VRP development was observed in a total of 16 patients among all groups. The mean duration before the development of VRP was 7.68±3.1 days. The number of hypo- (<60mg/dl) and hyperglycemic (>117mg/dl) events observed in the Leuven, CUP and Graz protocols were statistically compared, and no significant differ-

ence was observed (p>0.05). The comparison between groups regarding mortality revealed no statistically significant difference (p>0.05).

Appendix 1 - Leuven

TEST	RESULT	ACTION
Measure glucose on entry to ICU	BG>11.1 mmol/1?	Start insulin 2-4 IU/h
	BG 11.1 – 6.1 mmol/1?	Start insulin 1-2 IU/h
	BG<6.1 mmol/1?	Don't start insulin but continue BG monitoring every 4 h
Measure glucose every 1-2 h until normal range	BG>7.8 mmol/I?	Increase insulin dose by 1-2 IU/h
	BG 5.1 – 7.8 mmol/1?	Increase insulin dose by 0.5-1 IU/h
	BG approaching normal range?	Adjust insulin dose by 0.1-0.5 IU/h
Measure glucose every 4 h	BG approaching normal range?	Adjust insulin dose by 0.1-0.5 IU/h
	BG normal?	Insulin dose unchanged
	BG falling steeply?	Reduce insulin dose by half and check more frequently
	BG 3.3-4.4 mmol/1?	Reduce insulin dose and check BG within 1 h
	BG 2.2-3.3 mmol/1?	Stop insulin infusion, assure adequate baseline glucose intake and check BG within 1 h
	BG <2.2 mmol/1?	Stop insulin infusion, assure adequate baseline glucose intake, administer glucose per 10 g IV boluses and check BG within 1 h

Appendix 2 – Cup

1. Target glycemia is 4.5-6.5 mmol/1.
2. Before starting insulin infusion check plasmatic potassium level, if K < 4 mmol/1 consult ICU doctor
3. Before starting insulin infusion check other infusions for insulin
4. Standard dilution of insulin is 50 IU in 50 ml of saline solution
5. Before starting insulin infusion check if patient received s.c. insulin bolus or p.o. antidiabetics drug in last 12 hours
6. When parenteral or enteral nutrition is stopped, stop insulin (if not set alternatively)
7. Presumption is standard glucose intake, parenteral or enteral nutrition following protocol for nutrition

BASIC STARTING DOSAGE:

Blood glucose	Bolus iv. insulin (IU)	Starting insulin infusion rate (ml/h)
6.5 – 7.9	0	1
8 – 9.9	5	1
10 – 12.9	7	2
13 – 15.9	10	3
16 – 19.9	13	4
20 or more	15	5

In 2 hours after start of insulin infusion check glycemia, if:

Blood glucose	INTERVENTION	Check glycemia in
< 3.5	Stop insulin, give G40% 40 ml iv.- call for ICU doctor! Insulin at 1 ml/h with glycemia over 6mmol/l	1 hour
3.6 – 4.5	Stop insulin and call ICU doctor!	1 hour
4.6 – 5.0	Decrease by 1 ml/h	2 hour
5.1 – 5.9	Keep the same rate, if glycemia is stable in 2 following measurements, next level could be checked in 4 hours	2 hour
6.0 – 6.9	Increase by 0,5 ml/h	2 hour
7.0 – 7.9	Increase rate by 1 ml/h	2 hour
8.0 – 9.9	Increase rate by 2 ml/h	2 hour
10.0 –12.9	Bolus 5 IU, increase rate by 3 ml/h	1 hour
13.0 –15.9	Bolus 5 IU, increase rate by 4 ml/h	1 hour
16.0 –19.9	Bolus 10 IU, increase rate by 5 ml/h	1 hour
>20.0	Bolus 15 IU, increase rate by 5 ml/h	1 hour

If blood glucose drops by more than 8 mmol/l between 2 following measurements decrease rate to half and call for ICU doctor

Appendix 3 – Graz

The algorithm as implemented at MUG makes a difference between patients at the intensive care unit as is showed below. Patients with insulin-dependent diabetes receive insulin in the continuous infusion whereas patients without diabetes are treated by a bolus only insulin administration regimen.

1. Application of insulin
   a. Insulin infusion for all insulin dependent diabetic patients and TX-patients
   b. Insulin bolus for all other patients
2. Preparation of insulin infusion
   a. Standard concentration is 100 IU in 50 ml Voluven
   b. Solution is stable for at the most 24 h
3. Frequency of measurement:
   i. First measurement at admission
   ii. At least six measurements per day or 1-2 hourly if requested from treating physician
   iii. 60 minutes after each intervention (change of infusion rate or bolus)
   iv. 60 minutes after stop of glucose infusion or nutrition
4. Glucose target value
   a. ICU: 4.4 – 6.1 mmol/l (below 6.6 mmol/l)
   b. General ward: <11 mmol/l
5. Insulin Dosing Scheme
   a. Insulin Infusion
      i. BG>12,2 mmol/l (BG>220 mg/dl) 8 IU/h
      ii. 8,3 mmol/l<BG<12,2 mmol/l (150 mg/dl <BG<220 mg/dl) 6 IU/h
      iii. 6,7 mmol/l<BG<8,3 mmol/l (120 mg/dl <BG<150 mg/dl) 4 IU/h
      iv. 3,3 mmol/l<BG<4,4 mmol/l (60 mg/dl <BG<80 mg/dl) Insulin Stop
      v. 3,3 mmol/l<BG (60 mg/dl <BG) Insulin Stop + 10 g Glucose (20%) IV
   b. Insulin Bolus
      i. BG>12,2 mmol/l (BG>220 mg/dl) 8 IU
      ii. 8,3 mmol/l<BG<12,2 mmol/l (150 mg/dl <BG<220 mg/dl) 6 IU
      iii. 6,7 mmol/l<BG<8,3 mmol/l (120 mg/dl <BG<150 mg/dl) 4 IU
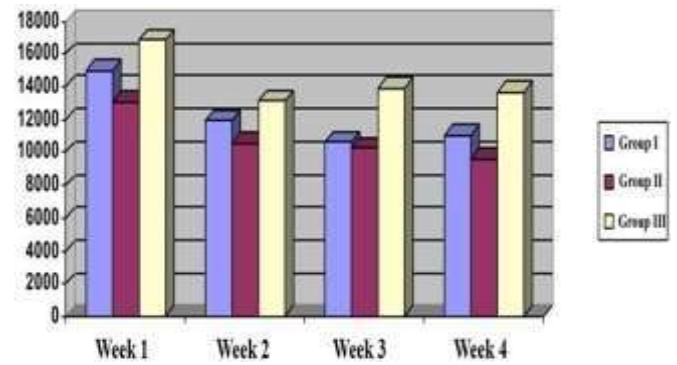
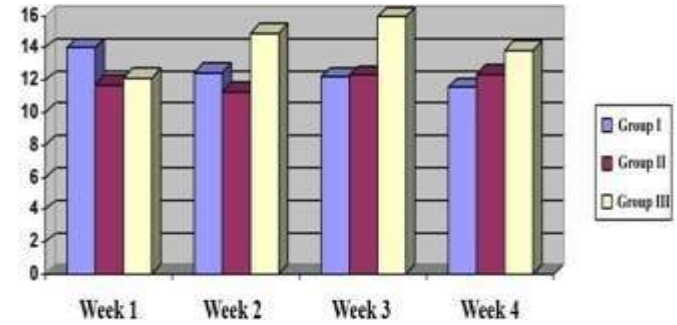Figure 1: Leukocyte counts.

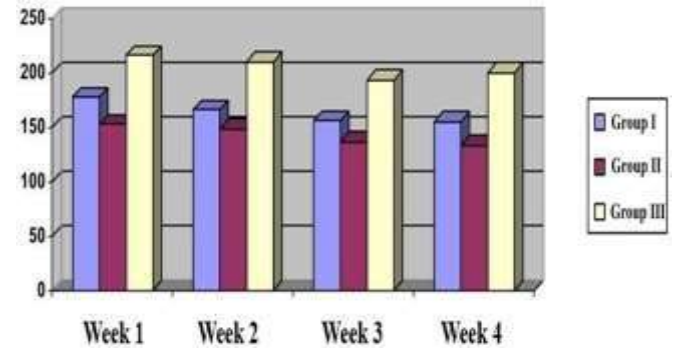Figure 2: CRP values.

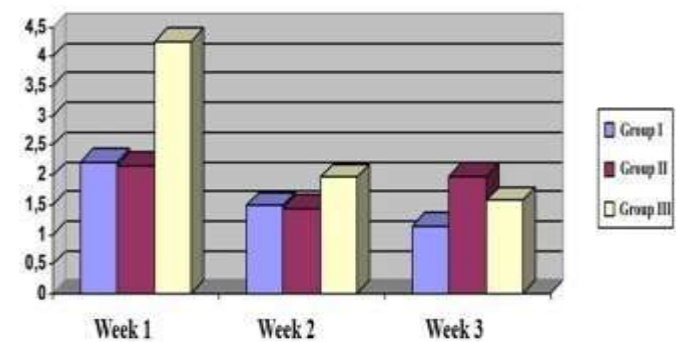Figure 3: Triglyceride levels.

Figure 4: Lactate levels.

Table 1: Infusion dose comparison between groups.

Protocol	Group I (Leuven) mean±SD	Group II (CUP) mean±SD	Group III (Graz) mean±SD	p Value
Insulin dose	432.30±641.75	489.90±475.08	328.70±361.07	0.772

SD= Standard deviation

6. Discussion

Critical patients that stay in the ICU more than 5 days carry an increased risk of sepsis, inflammation and critical polyneuropathy, which may, in turn, result in mortality. Hyperglycemia, which may be observed in either diabetic or non-diabetic patients with acute disease, has been determined to be either the reason or one of the side effects in many different clinical situations. It has been suggested in recent studies that hyperglycemia prolongs ICU stay and increases mortality rates [1,2].

In 2001, van den Berghe et al. conducted a study on 1.548 patients who were mechanically ventilated in the ICU of the University of Leuven, Belgium and 63% of whom had undergone cardiovascular surgery[3]. In that study, the treatment was targeted at maintenance of normoglycemia (80-110 mg/dl) via continuous intravenous insulin infusion. A total of 783 patients in the study receiving conventional therapy were administered insulin infusion when blood glucose levels were over 215 mg/dl. The group with intense insulin therapy were administered insulin infusion in order to maintain blood glucose level within 80-110mg/dl range. At the end of the study, mortality was decreased by 40% in the intense insulin therapy group, and decreased by 9.6% in the conventional therapy group[3]. The Leuven Study has facilitated the construction of glucose treatment protocols in ICUs worldwide and has been indicated as a reference in application standards [4,5].In the present study, as for the insulin infusion doses administrated within the 15-day follow-up period, there was no difference among groups.

Finney et al. reported that glycemic control had more favourable effect on mortality than the amount of exogenous insulin used[6].van den Berghe et al. compared the mortality rates in ICU patients with regard to blood glucose levels of <110 mg/dl, 110-150 mg/dl and >150 mg/dl, best outcomes were obtained in the <110 mg/dl group[7].However, this group had the highest risk of hypoglycemia as well. Hypoglycemia, which was found to be significant with regard to the development of neurological sequels, was detected to be 1.8% in the conventional and 11.3% in the intensive insulin therapy groups. Brindley et al. evaluated 1.200 patients with ICU stays for three or more days, the effect of intensive insulin therapy on the mortality of patients was investigated[8].It was demonstrated that intensive insulin therapy reduced the mortality rate compared to the conventional therapy group in patients staying in the ICU more than three days. In the present study, no difference was observed between groups regarding mortality. Our mortality rate was detected to be 50 percent and the high mortality rate was related to patients with comorbidities who stayed more than 5 days in the ICU.

The effective clinical outcome observed following insulin therapy has been related to the reduction in inflammatory mediators. It has been demonstrated that the reduction in CRP was concurrent with the beneficial effects of insulin[9].In a different series, including 1.548 patients receiving either intensive or conventional insulin therapy, mannose-binding lectin and CRP series were compared[10]. On the 5th day, CRP levels observed in the intensive insulin therapy group were significantly reduced compared to the conventional therapy group. On the 15th day, CRP levels were similar among the exitus patients between the two groups, whereas the CRP levels were significantly lower among the survivors in the intensive insulin therapy group, which was related to the prevention of hepatic acute phase response and, accordingly, increased inflammation. In the present study, no statistically significant difference was observed among groups regarding the CRP values.

Insulin has effects on lipids as well. It suppresses the lipoprotein lipase enzyme that hydrolysis the triglycerides into fatty acids and causes an antilipolytic effect. It increases the synthesis of triglycerides in liver and adipose tissue, facilitates the synthesis of free fatty acids and the esterification of triglycerides. Mesotten et al. compared 363 patients using conventional or intensive insulin therapy in the ICU with regard to blood lipid profiles and mortality[11].Cholesterol levels upon admission and during the ICU stay were similar between groups. Serumtriglyceride levels were similar upon admission; however, they significantly increased in the conventional therapy group on the 8th day and decreased in the intensive insulin therapy group. Furthermore, it was found that the HDL levels were reduced in both groups, whereas the reduction in the conventional therapy group was more significant than the intensive insulin therapy group. The LDL cholesterol levels showed a reduction in both groups at first and then an increase on the 8th day. This increase was reported to be more significant in the intensive insulin therapy group[11].In the present study, there was no difference in cholesterol levels among groups. However, 2nd, 3rd and 4th week cholesterol levels in the group with CUP protocol were significantly reduced compared to the 1st week cholesterol levels. No difference was observed among groups regarding triglyceride levels. HDL levels decreased in all three groups and no difference was observed among groups. LDL levels decreased compared to the baseline levels as well and similarly, no significant difference was observed.

Increase in blood lactate levels has been accepted as the indicator of insulin resistance[12]. In a study investigating the insulin and coronary sinus lactate levels in coronary artery surgery, the clinical outcomes were better in the patient group with high-dose insulin[13]. In the present study, no difference was observed in the 1st and 2nd week lactate levels measured throughout the ICU stay among three groups with similar baseline lactate levels but under different insulin protocols. All lactate levels measured in our patients were within normal ranges except those measured

on the day of admission.

Collier et al. reported 818 patients receiving inpatient therapy, insulin protocols were administered to 383 patients in order to provide normoglycemia and 435 patients were given antidiabetic drugs for glycemic control[14].In this study, which aimed to investigate the VRP, surgical wound infection and mortality, insulin infusion was performed when the blood glucose level exceeded 110mg/dl among patients on mechanical ventilation for more than 24 hours. The maximum blood glucose level was found on the 14th day and the rates of pneumonia and mortality were found to be significantly higher in the control group. Whenever the blood glucose level was higher than 150mg/dl on one or more days, the mortality rate was found to be increased by 2 to 3- fold. The authors have concluded that a blood glucose level of 150 mg/dl or higher was associated with a poor prognosis. In the present study, VRP was observed within the first 10 days in the 60, 50 and 50% of the patients in the LP, CUP and GP groups, respectively. An average of 7.68 days elapsed up to the development of VRP in all study groups.

Until recently hyperglycemia was controlled only when it reached the renal threshold of 12.0 mmol/L. After Leuven, many reconsidered their practice, attempting to more vigorously control blood glucose. The publication of normoglycemia in intensive care evaluation-survival using glucose algorithm regulation (NICE-SUGAR) trial called tight glycemic control protocols into question. Certainly, stress hyperglycemia is not an innocent bystander and is associated with an increase in mortality. The Leuven studies should be viewed as a "proof-of-concept" with future work aiming to optimize and confirm their findings[15]. Critically ill patients have high glucose variability due to the complex and poorly understood interactions of hormones and metabolites. The increased risk of hypoglycemia from attempting tight glycemic control must be obviated before any benefit is likely to be consistently seen.

7. Conclusions

The positive effect of intensive insulin therapy on normalizing hyperglycemia developed during the progression of critical diseases and on improving the outcomes of patients in ICUs, has prompted the determination of individual insulin protocols by each clinic. It was concluded that all three protocols analyzed in this study may be used for glycemic control and these protocols are similarly effective in reducing CRP values, regulating blood lipid profiles and reducing the development of ventilator-related pneumonia.

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