INTENSIVE INSULIN THERAPY IN SURGICAL PATIENTS WITH TYPE 2 DIABETES MELLITUS

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The aim of the investigation was to assess the efficiency of intensive insulin therapy in surgical patients with type 2 diabetes mellitus (DM 2) in intensive care unit in relation to the effect on postoperative clinical progression and 90-day survival of patients.

Materials and Methods. The study included 89 patients hospitalized in intensive care unit for various surgical pathologies, with DM 2 in past medical history. On admission the patients were divided into 4 groups in a random manner. First 72 h target glycemia range for groups 1 and 2 was glucose level of 6.5–8.5 mmol/L, and for groups 3 and 4 — 8.6–11.0 mmol/L. Continuous insulin infusion was chosen for the treatment of groups 1 and 3 for the same period, the patients of groups 2 and 4 were given divided insulin injections. The severity of all patients was studied first 24 h and 72 h after inpatient treatment according to APACHE II, SAPS II.

Conclusion. In ICU patients suffering from type 2 DM with various surgical pathology, target glycemic levels of 6.5–8.5 and 8.6–11.0 within the frame of one insulin therapy method are not associated with the differences in relation to the severity and outcome of the main pathology. Glycemic control in target range of 6.5–11.0 mmol/L by intravenous insulin infusion has the advantage over divided insulin subcutaneous injections regarding the severity and outcome of the main pathology.

Key words: type 2 diabetes mellitus; continuous insulin infusion; glycemia.

Diabetes mellitus (DM) can complicate the course of the most diseases including those requiring surgical management. Despite the fact that the complication risks of operative intervention in DM patients have decreased recently, a surgical intervention still remains dangerous for these patients [1–3]. Postoperative hyperglycemia is associated with higher morbidity of infectious complications [4, 5], sepsis [6, 9], etc. Significant increase of glucose level intraoperatively and postoperatively can force the development of life-threatening conditions, such as ketoacidotic coma, hyperglycemic hyperosmolar syndrome [10–12]. These are the reasons for determining an optimal glycemic level in this group of patients.

The prospective controlled randomized study "Leuvenstudy" included 1548 patients who had undergone cardiac surgeries. The patients of intensive care unit (ICU) were divided into two groups: conventional and intensive insulin therapy (IIT). In the group of conventional insulin therapy target glycemic level was 10.0–11.1 mmol/L, and in IIT group — 4.4–6.1 mmol/L. The authors showed the maintenance of blood glucose within the range of 4.4–6.1 mmol/L to have significant clinical advantages. Overall postoperative mortality was found to decrease — 4.4 versus 8.0%, and in patients who stayed in ICU for more than 5 days — 10.6 versus 20.2% [13]. However, similar studies [14–16] did not reveal significant reduction of mortality among ICU patients with IIT compared to the patients receiving conventional treatment, though they were found to have far less renal involvements, reduced time of artificial lung ventilation, as well as reduced stay in ICU and in hospital in general.

The results obtained by "Leuvenstudy" had a profound impact on insulin therapy standards in ICU patients; the standards were published in various guidelines and recommendations [12–14, 17–20]. NICE-SUGAR survey results [18] demonstrated the necessity of reconsideration of the approved standards and more detailed study of the problem. We compared two groups with different target glycemic levels in ICU patients: groups with intensive glycemic control (target blood glucose values — 4.5–6.0 mmol/L) and groups of conventional glycemic control (target blood glucose values — 8–10 mmol/L). In present study intensive glycemic control compared to conventional control was accompanied by mortality increase in adult ICU patients. After the correction for the main risk factors of unfavorable outcome the differences remained. Severe hypoglycemia (less than 2.2 mmol/L) also was found more frequently in the group of intensive control compared to the conventional control group.

The retrospective analysis of 1422 ICU patients with traumatic injuries also showed the advantage of moderate glycaemic control [16, 21]. A large number of investigations demonstrated the results, which did not confirm "Leuvenstudy" findings. It indicates the necessity of a more

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detailed study of the problem. Moreover, the study paid no attention to the modes of insulin administration in different target glycemic levels, though the problem is very important in medical practice.

The aim of the investigation was to assess the efficiency of intensive insulin therapy in surgical patients with type 2 diabetes mellitus in intensive care unit in relation to the effect on postoperative clinical progression and 90-day survival of patients.

Materials and Methods. The study included 89 patients hospitalized in intensive care unit for various surgical pathologies, with either DM 2 in past medical history, or hyperglycemia >11 mmol/L on admission. DM diagnosis was made according to WHO criteria (1999). Exclusion criteria were the following: type 1 DM, oncology, and ketoacidosis (Fig. 1).

On admission the patients were divided into 4 groups in a random manner. First 72 h target glycemia range for groups 1 and 2 was glucose level of 6.5–8.5 mmol/L, and for groups 3 and 4 — 8.6–11.0 mmol/L.

Continuous insulin infusion was chosen for the treatment of groups 1 and 3 for the same period, the patients of groups 2 and 4 were given divided insulin injections. We used Actrapid – rapid-acting insulin. For infusion 50 U of insulin were diluted in 50 ml of 0.9% saline solution and infused by syringe pump "Perfusorcompact B-I BRAUN" (Germany). Infusion rate was determined by capillary blood glycemia dynamics. A qualified person made the

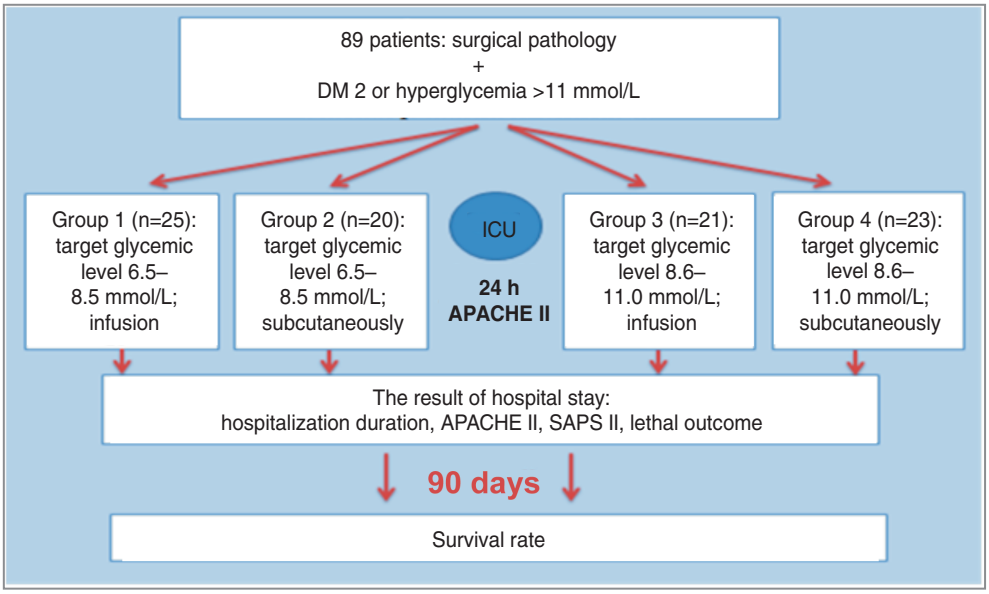

Fig. 1. Study design

The characteristics of groups at the moment of inclusion into the study, Me [25%; 75%]

Parameters	Target glycemic level, mmol/L				p
	6.5–8.5		8.6–11.0		
	Group 1 (n=25) — infusion	Group 2 (n=20) — subcutaneously	Group 3 (n=21) — infusion	Group 4 (n=23) — subcutaneously	
Age, years	69.0 (37.0–80.0)	64.5 (33-76.0)	60.0 (31–75.0)	72.0 (41–86.0)	0.052
Female	16	14	8	18	0.4
Male	9	6	13	5	
Number of hypertensive patients, %	76	75	78	81	0.96
Number of CHD patients, %	71	66	67	76	0.17
Body mass index, kg/m^2	26.1 (21.3–29.8)	22.4 (20.6–27.4)	28.4 (23.1–31.9)	24.7 (21.5–29.8)	0.25
DM 2 duration, years	7 (3–20)	6 (2–10)	8 (1–15)	6 (1–11)	0.63
HbA_1C, %	8.5 (7.3–11.3)	8.1 (7.4–10.7)	8.6 (7.5–9.7)	8.1 (7.1–9.4)	0.52
Hospitalization, days	14	20	16	16	0.09
APACHE II on admission, scores	22.3 (16.5–47.8)	20.9 (16.4–26.2)	21.1 (11.3–51.2)	18.9 (9.0–26.4)	0.16
APACHE II after ICU, scores	13.1 (6.5–36.3)	14.2 (6.0–19.3)	12.2 (5.0–25.6)	12.1 (5.6–19.5)	0.5
Saps II, scores	14.9 (7.0–28.5)	20.0 (13.2–28.5)	19.8 (17.5–23.8)	18.1 (16.5–24.9)	0.69
Glycemia on admission, mmol/L	17.1 (14.8–19.5)	16.0 (13.7–18.5)	16.9 (13.8–18.2)	15.8 (12.6–17.7)	0.9

measurements every hour using glucose meter Accu-Chek Performa, and followed up a patient within 24 hours. Subcutaneous Actrapid injections were given against the background of the preceding antihyperglycemic therapy (or its absence). Such an approach corresponded to the local working standards of managing the patients with surgical pathology and DM 2. Glycemic level in the groups was determined hourly.

The severity of all patients was studied within first 24 h and 72 h after inpatient treatment according to APACHE II (Acute Physiology and Chronic Health Evaluation), SAPS II (New Simplified Acute Physiology Score), and general clinical examination (past history, physical data). The patients were reexamined 90 days after the discharge from hospital. We estimated the survival rate of patients in both groups.

The groups under study did not differ in gender, the character of surgical pathology, the severity according to APACHE II, SAPS II. There were no statistically significant differences according to the main DM 2 characteristics as well (See Table). The patients did not differ significantly in surgical pathology. In all 4 groups there were patients with acute cholecystitis, acute pancreatitis, pancreonecrosis, diabetic foot, bowel obstruction, and other pathology.

The data were statistically processed using software package Statistica 6.0. We calculated median (Me) and interquartile interval (25–75%) when describing the data, the distribution of which differed from that of Gaussian. If the distribution differed from normal, we used the criteria of Mann–Whitney, Wilcoxon, and Kruskal–Wallis test; rate difference in independent data sampling was calculated using Fisher-test and χ^2 Pearson's coefficient.

Results and Discussion. In all groups target glycemic levels were reached within first 24 h: in group 1 — in 8 (3–9) h, in group 2 — in 21 (8–24) h, in group 3 — in 5 (1–6) h, in group 4 — in 9 (4–10) h, (p=0.045). Severity dynamics according to APACHE II was determined in 72 h (Fig. 2).

The assessment of severity dynamics according to APACHE II revealed no statistically significant difference in all groups. Thus, target glycemic levels do not have significant influence on the patients' severity dynamics.

The comparison of the groups with different insulin administration revealed statistically significant difference in severity dynamics according to APACHE II (p=0.024) (Fig. 3). However, the comparison of the values in groups 1 and 2, as well as groups 3 and 4 did not show any significant difference (p=0.39)

Thus, insulin therapy mode, rather than target glycemic level, has a significant impact on severity dynamics according to APACHE II. We stated that continuous insulin infusion resulted in significant improvement of the patients' severity compared to divided subcutaneous injections. Moreover, in groups with lower target glycemic values (6.5–8.5 mmol/L), insulin infusion had the tendency for higher increase according to APACHE II compared to the groups with target level of 8.6–11.0 mmol/L.

Lethal outcome in hospital in group 1 was 4%, in group 2 — 20% (p=0.22), in group 3 — 0%, in group 4 — 17% (p=0.13).

Survival in patients 3 months later in group 1 was 96%, in group 2 — 50% (p=0.001); in groups 3 and 4 it went as low as 95.2 and 52.1%, respectively (p=0.004). The survival estimate 3 months later showed statistical significant difference between the groups 1 and 2, as well as between the groups 3 and 4 (Fig. 4).

However, the comparison of survival in groups 1 and 2, as well as groups 3 and 4 did not show statistically significant difference. The comparison of groups 1 and

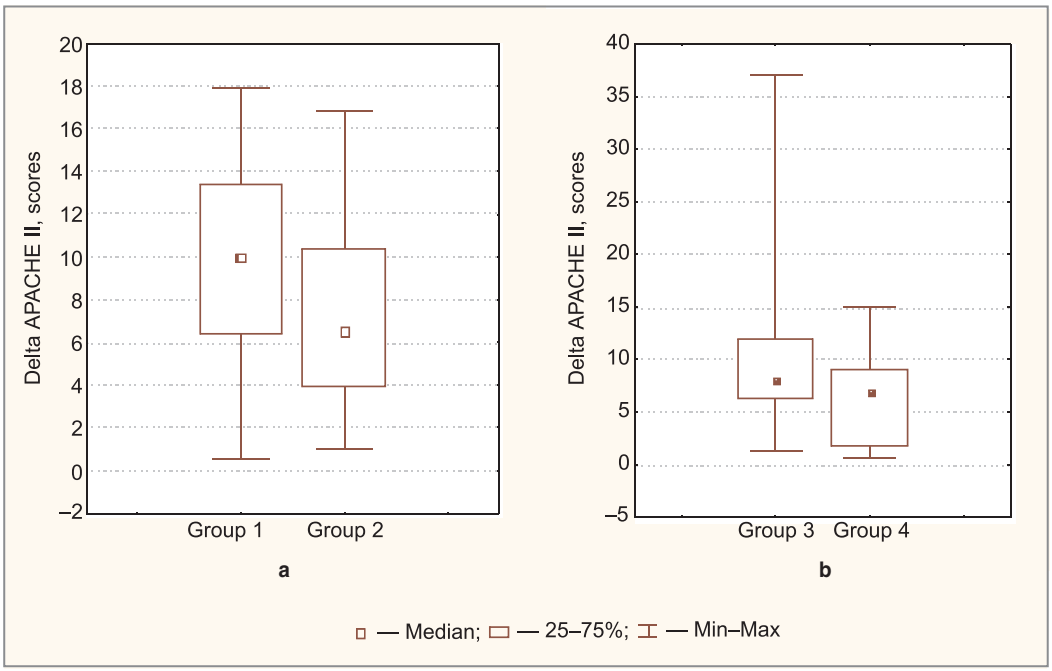

Fig. 2. ICU patient severity dynamics 72 h later: *a* — in groups 1 and 2, p=0.13; *b* — in groups 3 and 4, p=0.22

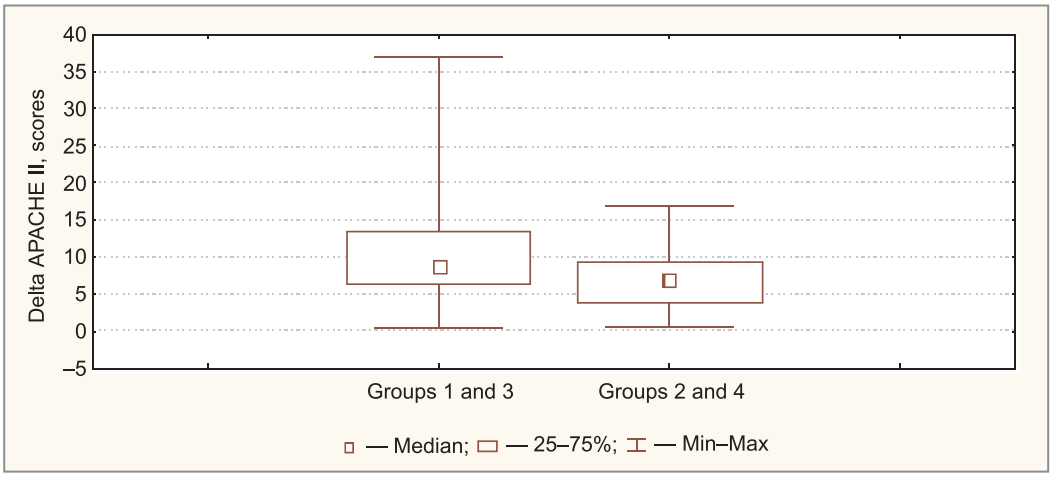

Fig. 3. The severity dynamics of ICU patient 72 h later in groups with different insulin therapy methods

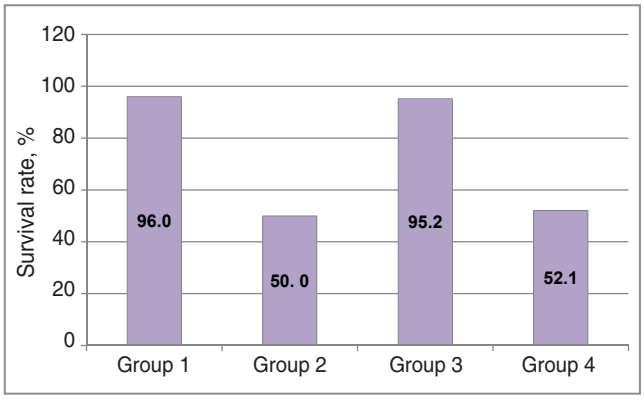

Fig. 4. Survival rate 3 months later in the groups (p=0.001)

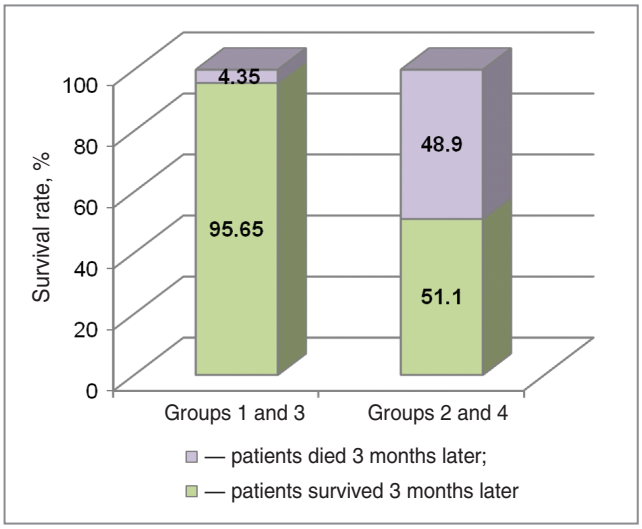

Fig. 5. Average survival rate in groups with different insulin therapy modes 3 months later (p=0.001)

3, as well as 2 and 4 in these parameters demonstrated statistically significant difference (p=0.01) (Fig. 5).

In addition, within 72 h hypoglycemic event rate in the groups was statistically significantly different. In group 1 the number of biochemical hypoglycemias was 32%, in group 2 —85%, in group 3 — 19%, in group 4 — 26%. The comparison of groups 1 and 2 with the same target glycemic level (6.5–8.5 mmol/L) revealed statistically significant difference in the number of biochemical hypoglycemias (p=0.002).

It indicates that continuous insulin infusion is a safer mode in lower target glycemic levels (6.5–8.5 mmol/L).

Conclusion. In ICU patients suffering from type 2 DM with various surgical pathology, target glycemic levels of 6.5–8.5 and 8.6–11.0 within the frame of one insulin therapy method are not associated with the differences in relation to the severity and outcome of the main pathology. Glycemic control in target range of 6.5–11.0 mmol/L by intravenous insulin infusion has the advantage over divided insulin subcutaneous injections regarding the severity and outcome of the main pathology.

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