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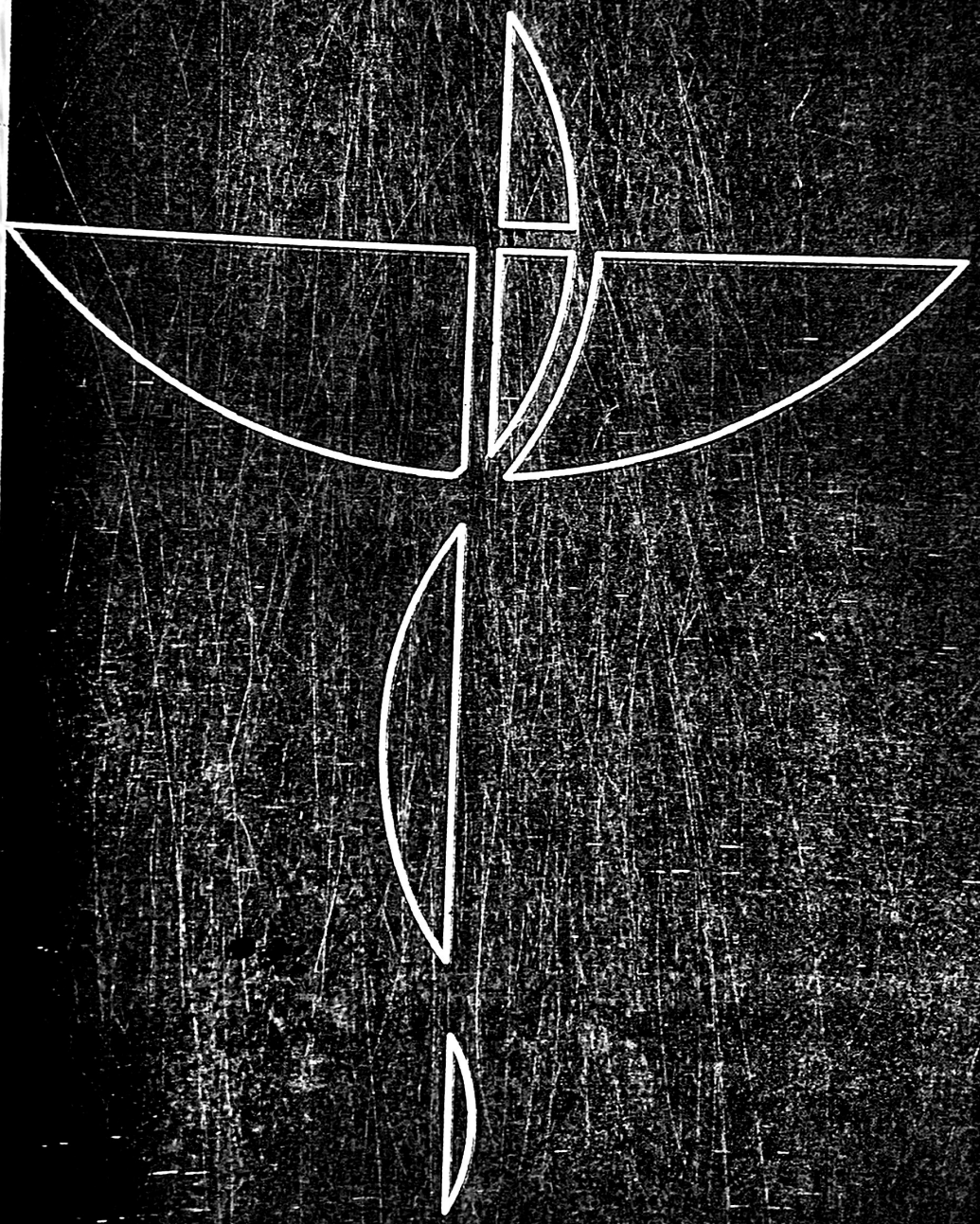

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EFFECTS OF PREOPERATIVELY GIVEN AMINO ACID INFUSION ON BLOOD GLUCOSE AND C-PEPTIDE LEVES IN SURGICAL PATIENTS

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Abstract

Introduction: Surgical patients have increased stress response that impact glucose metabolism. Preoperative fasting emphasizes the stress response and promotes stress hyperglycemia. Protein- reach food in diabetics has positive influence on glycaemia and insulin secretion. Therefore preoperative change from "hunger" to "fed" with amino acid infusions may be beneficial for patients who have the risk for developing hyperglycemia.

Aim of this study was to evaluate whether preoperative infusion of amino acids influence and how the same affect serum glucose and C -peptid.

Material and Methods: Study included 13 patients scheduled for minor surgery, aged 25-50 years, without diabetes, with preoperative values of $HgA_1C \leq 5.7$ % and glucose ≤ 6.1 mmol/l, divided into two groups. Two hours prior surgery, patients in Group AA (n=6) received infusions of amino acids with volume of 12ml/kg for period of 120 minutes, whereas patients in control group (group RL) received Ringer Lactate with same protocol. C-peptide and blood glucose levels in both groups were measured: before the start of infusion (T1), after the expiry of infusion (T2) and 24 hours postoperatively (T3).

Results: Both groups showed increase of blood glucose for T2 (5.26-5.42 vs 5.31-5.42). Postoperatively (T3),average blood glucose levels decreased in group AA to 4.65 and increased in RL group to 5.7 respectfully. Postoperative there was significant difference in blood glucose between the two groups (p = 0.007). The value of C-peptide increased progressively in group AA (1.33-1.63) while in RL decreased (1.31 -1.1). Between the groups, values of C-peptide showed no significant difference (p> 0.05).

Conclusion: Preoperative administration of amino acids in surgical patients improves blood sugar levels and increases C-peptide levels.

Keywords: Amino acids, preoperatively, glucose, C-peptide, surgical patients.

ВЛИЈАНИЕ НА ПРЕДОПЕРАТИВНО ДАДЕНИ АМИНО КИСЕЛИНИ ВРЗ НИВОТО НА ГЛИКЕМИЈА И Ц-ПЕПТИД КАЈ ХИРУРШКИ ПАЦИЕНТИ

Абстракт

Вовед: Хируршки пациенти имаат индуциран стрес одговор кој доведува до промени во метаболизмот на гликоза. Предоперативното гладување ги нагласува овие промени и промовира стрес хипергликемија. Исхраната богата со протеини кај пациенти со дијабетес влијае позитивно врз гликемијата и лачењето на инсулин. Според ова, предоперативната промена на состојбата од "гладна" во "нахранета" со

амино киселини може да биде од корист за пациентите кои имаат ризик од гликемиски нестабилности.
Цел на оваа студија беше да се оцени дали предоперативна инфузија со амино киселини влијае и како влијае врз серумското ниво на гликоза и Ц-пептид.
Материјал и методи: Студијата вклучуваше 13 пациенти закажани за мала, елективна оперативна интервенција, на возраст од 25 до 50 години, без дијабетес, со вредности на HgA1C ≤ 5,7% и гликемија ≤ 6.1 mmol / l поделени во две групи. Пациентите од групата АК, два часа пред операција добија инфузии од амино киселини со волумен од 12ml/kg за период од 120 минути, додека кај пациентите во контролната група (група РЛ) со ист режим се аплицираше Рингер Лактат. Кај двете групи, нивото на Ц-пептид и гликемија се одредуваа: пред почетокот на инфузија (Т1), по истекот на инфузија (Т2) и 24 часа по операцијата (Т3).
Резултати: Кај двете групи на пациенти се регистрираше пораст на гликемијата во Т2 (5,26-5,42 vs 5,31-5,42). Постоперативно (Т3), просечното ниво на гликемија се намали во групата АА до 4.65 mmol/l, а во контролната група се зголеми на 5,7 mmol/l. Постоперативните вредности на гликемија меѓу групите покажаа сигнификантна разлика (p = 0.007). Вредностите на Ц-пептид во групата АА растеа од Т1 до Т3 (1,33-1,63), додека во контролната група се намалуваа (1,31 -1,1). Меѓу групите, вредностите на Ц-пептид не беа статистички различни.
Заклучок: Предоперативната администрација на амино киселини кај хируршки пациенти го нормализира нивото на гликемијата и го зголемува нивото на С-пептид.
Клучни зборови: Амино киселини, предоперативно, гликоза, С-пептид, хируршки пациенти.

Introduction

In the era of evidence based medicine, it is quite clear that all surgical patients have increased stress response which carries the risk of blood glucose dysregulation. During surgical trauma majority of metabolic changes are proportional to the size of injury [1, 2]. Contrary, for blood sugar changes it is still not clear whether they are related only to the size of the trauma or they are result of preoperative starvation and therapeutic fluid regime [3, 4, 5]. However, glycemic variations and occurrence of stress hyperglycemia have detrimental effect on patients' outcome.
The size of the surgical trauma in most cases is a factor that cannot be influenced or changed. This fact usually leaves other factors (such as preoperative fasting, anesthesia techniques and fluid therapy) to be the only factors that can be modulated by the anesthesiologists in order to improve glycemic control.
Preoperative fasting protocol NPO (Nothing Per Os) for 8 hours reduce the risk of pulmonary aspiration and it is a routine procedure for all surgical patients. NPO protocol emphasizes the stress response to injury and affects postoperative outcome[3]. Any kind of starvation makes changes of insulin/glucagon ratio and leads to lack of insulin. In the last decade, scientist debate that glycometabolic dysfunction is directly related to this protocol [3, 6, 7]. In this context, special place for caloric valued solutions (intravenous or oral) should be found as substitute for preoperative fasting or as a complement to standard crystalloid solutions.
Different therapeutic fluids have different impact on glycaemia [4, ,5, 8]. Crystalloids, which are considered as golden standard for surgical patients in per-operative period, have no influence on insulin secretion [4, 5, 9, 10]. On the other hand, amino acids which are reserved

for postoperative period (as protein spearing therapy) have strong insullotropic effect [11, 12]. Amino acids are metabolites and substrates, which allow their use in different stages of organic stress[13].

In various endocrinal studies, it has been proven that protein meal has insulotropic physiological effect and a diet reach in protein may have a protective effect on the occurrence of postprandial hyperglycemia [10]. Referring to diabetic patients, increased levels of amino acids (directly or as a product of protein metabolism) stimulate secretion of insulin [10, 12] or C-peptide [10]. Insulin is released in equimolar quantities with C-peptide [10, 14, in order to improve protein synthesis and utilization of amino acids from muscle cells. As a result of amino acid stimulation blood glucose levels remain stable [12, 13, 15]. Therefore, use of amino acids in preoperative period may take important as fluid therapy in patients who are imposed at risk for developing stress hyperglycemia (as surgical patients) [16, 17].

Maintaining glycemic homeostasis in preoperative and postoperative period is a real challenge. Many observational and intervention studies have confirmed that the maintenance of stable and optimal level of blood glucose in surgical patients reduces morbidity and mortality [16, 17, 18, 19].

Purpose

The aim of this study was to evaluate whether preoperative infusions of amino acids influence and how they influence on the levels of glucose and C-peptide in surgical patients.

Material and methods

This is a randomized prospective clinical study conducted at the RE KARIL- Clinic for Traumatology, Orthopedic diseases, Anesthesia, Reanimation and Intensive Care - Skopje, from January to June 2013.

Study included patients scheduled for minor elective surgery under general endotracheal anesthesia (OETA), aged 25-50 years, with no personal or family history of diabetes, with preoperative values HgA1C ≤ 5.7 % and glucose ≤ 6.1 mmol / l. Apart from the above mentioned criteria for inclusion in the study, patients should have BMI of less than $35m^2$ and belong to ASA I/II (physiological score for preoperative assessment of health according to American Society of Anesthesiologists).

Patients with endocrine disorders, patients with corticosteroid therapy (in any form), and patients who had weight loss larger than 7 kg (in the past two months) were excluded. From commenced study, patients whose operative intervention lasted longer than 2 hours, patients in whom corticosteroids, vasopressors, dextrose or transfusion therapy were added preoperatively were further excluded from analyzes.

Patients were randomly assigned in two groups. In the experimental group (gr. AA) patients received amino acids * solutions with 12 ml/ kg for 120 min. Composition of amino acids was as follows: alanine 15gr, 5.10gr phenylalanine, leucine 7.4gr, proline 15gr, arginin12 g, 6.6gr lysine, isoleucine 5gr, threonine 4.4gr, 14 g of glycine, histidine 3gr, 4.3gr methionine, valine to total 6.2gr with energy value of 440 kJ/1000ml. In the control group (gr. RL) with the same regime patients received Ringer Lactate.

All patients had preoperative standard NPO and premedication with 5mg Diazepam. Standardized intravenous anesthesia protocol was commenced for both groups. Induction was accomplished with fentanil (3µg/kg) and propofol (2mg/kg). Intubation was facilitated with rokuronium bromid 0.5mg/ kg. Anesthesia was maintained with continuous infusion

of propofol 6mg/kg /h. Patients were mechanicaly ventilated with inhaled fraction of a mixture of 50% O2 and 50% air.

In both groups we measured concentration of C-peptide and blood sugar. Samples were collected three times: preoperatively- before infusion the start of infusion (T1), after infusion ended (T2) and 24 hours postoperatively (T3).

The analysis of samples was performed at the Clinic for endocrine diseases, Skopje. The concentration of C-peptide was determined with ECLIA chemiluminescence (ELIKSIR 2010 Roshe; 0.53-2.9 ng.ml-1) while blood glucose was determined by glucose-oxidase method (Randoks, UK) with reference values 3.3-6.6 mmol/l.

The databases were created with the support of computer programs whose processing is done with standard descriptive and analytical methods bivar. Atributive and numerical data were analyzed using the coefficients for relationships, proportions or measure of central tendency. Statistical significance was tested with the Studentov t-test. Significance as indicated in $p<0.05$.

Results

By default criteria, in the study seventeen patients were included and randomized in two groups. Due to various reasons (listed above) and at different periods of the study, several patients were excluded, remaining total number of 6 patients in the AA group and 7 patients in the RL group. Randomization algorithm is shown in Figure 1.

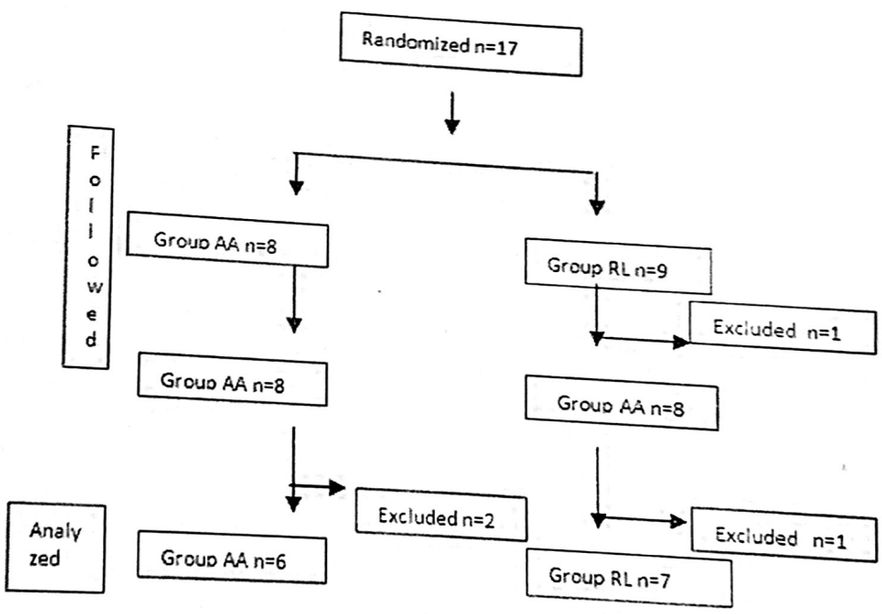


Figure 1 Chart of randomization

Among both groups of patients there were no statistically significant difference in demographic characteristics (ethnicity, age, gender, weight, height, BMI, ASA). Demographic and clinical characteristics are shown in Table.1.

Table 1 Demographic and clinical features

	Group AA (n=6)	Group RL(n=7)
Age	45.8±12.5 SD	44.8±8.1 SD
Gender		
Female/male	3/3	4/3
BMI(m^2)	26.67±5.28 SD	26.43±6.3 SD
ASA		
1	3(50%)	3(42.9%)
2	3(50%)	4(57.1%)
Lab.results	Mean	Mean
Le/Er/Hb/Tr	7.8/4.6/132/250	7.4/4.5/134/250
Ure/crea	5/66	4.7/58.5
Duration of surgery (min)	78.83±3.21 SD	81.42±14.32 SD

Abbreviations: AA-Amino Acid; RL- Ringer Lactate, SD-Standard Deviation

Tu mammae was the most frequent diagnosis in both groups. Average time period of the NPO between the two groups (8h and 80 + 24.49 SD (min) vs 8 h and 115 +22.58 SD (min) was significantly different (p = 0.02).
No anesthesiologcal complication or side effect was reported in both groups.

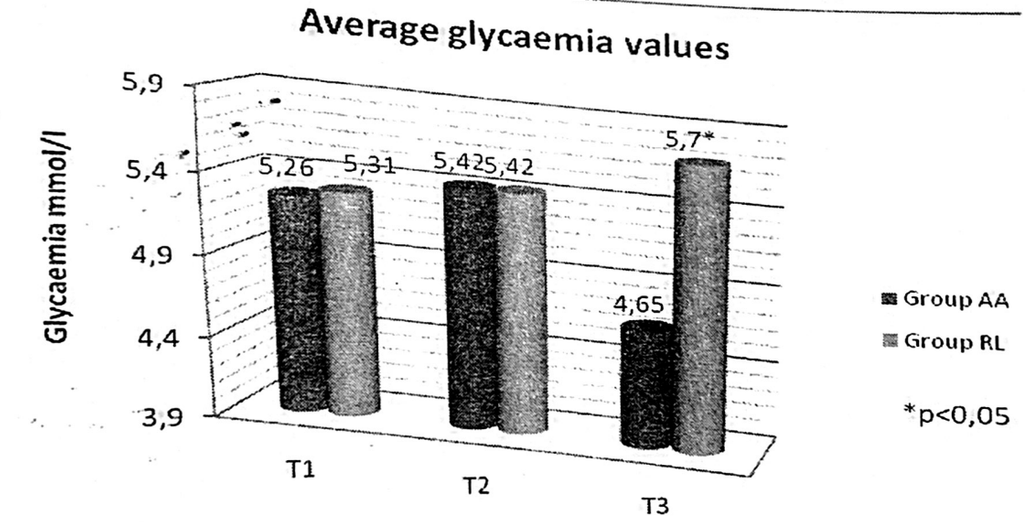
Blood glucose values varied in both groups patients. In AA group, average blood glucose values increased from 5.26mmol/l (T1) to 5.42mmol/l (T2) while in T3 reduced to 4.65mmol/l. In RL group, the blood glucose values progressively increased from T1 to T3 (5.31-5.7mmol/l). The lowest, individual value for glucose (3.9mmol/l) was recorded in the gr. AA in T3, while for the same time in the RL group the highest individual value (6.3) was registered Table.2
Inside the AA group significant difference (p = 0.002) for the average blood glucose values was registered between T2 and T3, and T1 and T3 (p = 0.008). Inside the RL group, significant difference (p = 0.01) was registered between average blood glucose values for T1 and T3.

Values of blood glucose over 5.8mmol/l, was registered only in RL group with 14.28% of patients in T2 and 42.86% in T3.
Between the groups significant differences in average blood glucose values were found in T3 (p=0.007).

Table 2 Average blood glucose values

Gr	Blood glucose	n	mean	max	min	Ste.Dev.
AA	T1	6	5.26	6.1	4	0.87
	T2	6	5.42	5.8	5	0.33
	T3	6	4.65	5.5	3.9	0.61
RL	T1	6	5.31	5.9	4.6	0.50
	T2	6	5.42	5.9	4.6	0.45
	T3	6	5.7	6.3	4.9	0.48

Abbreviations: AA-Amino Acid; RL- Ringer Lactate; T1 – time 1(before the start of infusion); T2-time 2 (after the expiry of infusion); T3- time 3 (24 hours postoperatively



Abbreviations: AA-Amino Acid; RL- Ringer Lactate; T1 – time 1(before the start of infusion); T2-time 2 (after the expiry of infusion); T3- time 3 (24 hours postoperatively);-p<0.05 between the both groups.*

Figure 2 Group differences for the average values of glucose

The average values of C-peptide in both groups varied. In gr. AA, average values increased from 1.33 (T1) to 1.63 ng.ml-1 (T3). In T3 in this group we found the highest individual

value for the C-peptide (2.4 ng.ml-1) in the whole study. In group AA, significant difference ($p = 0.007$) in average values of C-peptide occurred in T1 and T3.
In RL group, C-peptide average values progressively declined from 1.31 (T1) to 1.2 ng.ml-1 for T3, when lowest individual value was measured in the study.
Between the groups, the average values of C-peptide were not significantly different for any of the measurements.

Table 3 Average values of C-peptide between groups

Variable	Group AA	Group RL	p
C-peptide(ng.ml-1)	Mean +SD	Mean+SD	
T1	1.33 ± 0.35	1.31 ± 0.45	P=0.9
T2	1.51 ± 0.46	1.27 ± 0.33	P=0.2
T3	1.63 ± 0.40	1.1 ± 0.33	P=0.05

Discussion

The presented study was conducted as a pilot study in order to gain insights on the impact of the preoperative given amino acid solutions on the levels of blood glucose and C-peptide in surgical patients with minor surgical trauma.

In our study, blood glucose levels changed in both groups. All patients after receiving infusions had shown rise in blood sugar. This result is expected for patients receiving infusions with caloric value, but it was surprising for patients receiving Ringer lactate. Maitra[20], claims that blood glucose rise in the first, second and third hour from the initiation of any infusion (0.9% NaCl, 5% dextrose or Ringer Lactate). Unlike in our study, his results were collected during upper abdomen surgery which is considered as major surgical trauma.

On the other hand, Billiodeaux.DZ [4] and collaborators argue that giving Ringer Lactate does not affect blood glucose even in diabetic patients with diabetes type 1. In two clinical studies that have dealt with the preoperative administration of various therapeutic fluids in children and women (scheduled for minor surgery), the authors concluded that in total 36% of the patients who received Ringer's Lactate, blood glucose values were not affected in terms of rising on contrary they declined [5, 8].

In our study, in RL group postoperative blood glucose values are significantly different and higher than average blood glucose values in the Amino Acid group (4.65 vs 5.7mmol / l). Unlike this, Zhong J. et al. found that larger increase in blood glucose occurs in patients who receivied amino acid preoperatively [21].

The literature is clear that magnitude of surgical trauma is factor that affects the glycemic values [2]. In many cases anxiety, fear and chronic preoperative stress may contribute to increased blood glucose levels. In our study, all results that were obtained were excluded from direct surgical stimulus. Potential factors like: fear and anxiety were attenuated in all patients with standardized preoperative oral premedication with diazepam, which additionally attenuates hyperglycemic response [22].

Amino acids and sugar solutions given before and during surgery are considered as an additional source of exogenous glucose [12, 13, 15]. This seems to be true in our study if we discuss the parallel increase of blood glucose values in both groups after patients have received both infusions (T2). Unlike this, postoperative values of glycaemia rise only in patients receiving Ringer lactate. This suggests that this group of patients have some additional stimulus for generating endogenous glucose. It is clear that the same stimulus, prolongs its influence postoperatively. In our study, both groups of patients received infusions with the same regime and volume, leaving the differences in results only to be due to the fact that AA group beside of volume substitution had caloric substitution.

In 1986 Keane & Murray [23] discussed that patients with minor surgical trauma receiving preoperative infusions had shorter hospital stays and less complications. Fluid therapy is an alternative way of compensating volume deficit (caused by pre-operative starvation), but did not compensate caloric deficit.

During starvation ratio insulin/glucagon is changed. Without intervening with nutrients in this situation (to change from "hunger" to "fed" state), fast glycogenolysis and gluconeogenesis starts and stress hyperglycemia is pronounced. [3, .24, 25, 26].

Similar to our study, authors Ljunqvist O [24], Faria MS [19], Perrone F [15] proved that pre-operative administration of various nutrients greatly reduces postoperative blood glucose and insulin resistance. Some studies indicate that giving amino acid solutions in patients is associated with better postoperative outcome due to their positive glycoregulatory impacts [27, 28].

The advantage of pre-operative amino acid providing, versus standard crystalloid solutions is that nutritients accelerate insulin secretion via increased protein anabolism [17, 19]. This is a powerful mechanism that counteracts the development of hyperglycemia.

American College of Endocrinology (ACE), American Association of Clinical Endocrinology (AACE) and the American Diabetes Assotiation (ADA), recommend that the optimal values of glycemia in hospitalized patients should be 4.4 -5.6 mmol / l [29]. For each value beyond these limits it is strongly recommended to apply therapeutic intervention.

Levetan C [30] and Umpierrez GE [31] show evidence that in all hospitalized patients without diabetes, hyperglycemia will occur in about 38%. In our study postoperative, hyperglycemia (> 5.8 mmol/l) was recorded in 42.86% of patients only in group that received Ringer Lactate. This certainly indicates that amino acids reduce the occurrence of hyperglycemia.

Simultaneous measurement of blood glucose and C-petptid give a valid picture for pancreatic cells function referring to the insulin secretion and its utilization. C-peptide is released from secretor granules into the blood in equimolar amounts to insulin amounts. C-peptide is a substitute for the function of the beta cells and is used in the classification of diabetes [8, 14].

Higher values of C-peptide, indicate good beta cell function. In our study values of C-peptide increased progressively in AA group from preoperative 1.33 to 1.66 postoperative. On contrary, in RL group, its level progressively decreased from 1.31 to 1.24 ngrml-1.

Although the differences did not show any significant difference in the groups nor between groups, what can be discussed is the direction of variation.

In our study it is evident that patients who have preoperative caloric intake have rise in C-peptide values. Increased level of C-peptide indicates improved function of the pancreas that has ability to increase insulin secretion. If "diabetes trauma" [13] develops during surgery, pancreatic reserves are spent and secretion of C peptide decreases [8] (as is the case with Ringer Lactate group).

Most often reason for hyperglycemia in surgical patients is related to increased level of anti-insulin hormones and relative insulin deficiency. Researchers and clinicians are challenged to find adequate way to increase insulin stimulation and decrease occurrence of hyperglycemia, which is a real puzzle. Perhaps part of this puzzle is preoperative nutrition.

This study has several potential shortcomings. The number of respondents is small, but despite changes in blood glucose levels are evident. The second drawback is perhaps not standardasied surgical procedures. All surgical procedures have minor surgical trauma for sure. The study would allow better insights into the glicometabolic disturbances if it also investigates the level of insulin resistance. Right here we can draw recommendations for future research.

Although our study is small there are some benefits from it. The study allowed us to view the impact of preoperative nutrition with amino acids in surgical patients and we opened a new door in the larger study. If the results are confirmed in larger clinical study, applicability of this method in everyday anesthesiology practice will be great.

Conclusion

Preoperative administration of amino acids significantly improves blood glucose level and decrease occurrence of hyperglycemia in surgical patients. This, course should be confirmed in a large randomized clinical study.

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