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Parenteral Nutrition and preOp preparation in prevention of post-operative insulin resistance in gastrointestinal carcinoma

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ABSTRACT

Purpose: The aim was to compare preventive effect of total parenteral nutrition (TPN) and oral nutrition (preOp) on the perioperative insulin resistance prevention in surgical gastrointestinal cancer patients.
Material/Methods: The study was conducted in a group of 75 elective gastric and large intestine cancer patients. Patients were randomly divided into 3 study groups, 25 patients each: group I (NIL) - no preparations influencing tissue sensitivity to insulin, group II (TPN) - total parenteral nutrition in its preoperative stage and group III (TPN + preOp) parenteral nutrition and preOp in the preoperative phase.
Results: Immediately after the surgery, no statistically significant differences in insulin resistance level between groups were observed. During the first 6 postoperative hours, a statistically significant decrease of insulin resistance level in the TPN+ preOp group in comparison to others, was observed. During the first 24 postoperative hours, the NIL group was the only one to keep the insulin resistance level the same as in the preoperative phase.
Conclusions: Application of TPN in the preoperative phase leads to shortening of perioperative insulin resistance time. Combining TPN with oral application of carbohydrate before surgical procedure is an effective and the best method in postoperative insulin resistance syndrome prevention.

Key words: Total parenteral nutrition, preOp, insulin resistance, gastric cancer, large bowel cancer

INTRODUCTION

Insulin resistance can be defined as a decreased sensitivity of peripheral tissues on insulin. It is measured by ratio of insulin concentration on a particular cell to assimilation level of glucose dependent on this ratio. Another definition states that insulin resistance is a condition of impaired biological response of tissues to endogenous and exogenous insulin with regard to metabolism of carbohydrates, lipids or proteins [1-4].

The causes of appearance of clinical manifestations of insulin resistance have not been clearly defined yet. In 1877, Claude Bernard presented the issue of glucose metabolic disorders appearing in case of hemorrhage [4]. The next theses were written in the 90s of the 20th century. They touched upon the issue of carbohydrate metabolic disorders in elective surgery of inguinal hernia and laparoscopic cholecystectomy [4-7].

The aim of this study was a prospective research in order to compare the influence of intravenous (TPN – total parenteral nutrition) and oral (preOp) preparations in perioperative insulin resistance prevention in surgical gastrointestinal cancer patients.

Additionally, the following were evaluated:

- the influence of standard oral nutrition in hospital conditions on perioperative insulin resistance level;
- the effectiveness of TPN as an addition to oral nutrition in hospital conditions on prevention from perioperative insulin resistance;
- the effectiveness of TPN + preOp preparation completing oral nutrition in hospital conditions on prevention from perioperative insulin resistance

MATERIAL AND METHODS

The prospective, random study included 110 elective gastric and large intestine cancer patients treated in II Clinic of General and Gastroenterological Surgery of Medical University of Bialystok between 2008-2009. The patients were selected according to similar range of performed resection procedures and regional lymphadenectomy as well as the duration of the procedure itself, which approximately lasted for 3.5 hours. Additional clinical and biochemical criteria required for further research examinations included:

- BMI ratio > 20.5;
- Hemoglobin level Hb > 11 g/dl, total protein > 6.0 g/dl and plasma albumins > 3.8 g/dl in the serum. The analyses were performed 5 days prior to surgical procedure.

Criteria of exclusion from the research:

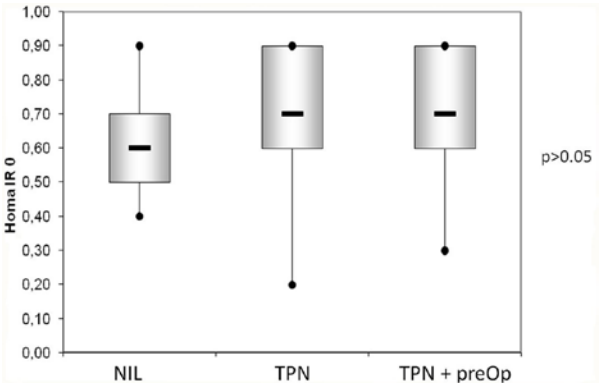
- Frank diabetes;
- Preoperatively diagnosed resistance to insulin;
- Stomach emptying disorders (absolute contraindications for preOp application);
- Undernourishment (according to SGA and NRS 2002).

Diabetes was excluded on the basis of performed oral glucose tolerance test (OGTT) while perioperative sensitivity to insulin was marked with modified HOMA IR index.

Out of 110 patients, 35 were excluded: 15 patients were diagnosed with a coexisting diabetes, 10 patients with high level of preoperative insulin resistance, 6 suffered from stomach emptying disorders and 4 were disqualified due to severe postoperative condition and therefore necessity of extended respiratory therapy. *Fig. 1* shows patient qualification for the research.

Finally, 75 patients were qualified for the research, 38 male and 37 female. The average age of these patients was 66 years. In 45 patients the carcinoma was located in their stomach and in the remaining 30 – in their large intestine.

Figure 1. **HOMA-IR factor before surgical procedure.**



Study groups

The patients qualified for insulin resistance research were randomly divided into 3 study groups consisting of 25 patients each. *Tab. 1* shows a comparative analysis of demographic data of the study groups in which the age, gender and type of illness pattern was similar.

Group I (NIL) consisted of 25 patients who received no preparations influencing the perioperative insulin resistance level. These patients had standard hospital meal for 4 days prior the operation. They received the last meal at night before the surgery. Oral nutrition were interrupted by fasting period due to performed diagnostic examination. Group II (TPN), consisted of 25 patients, who in addition to the standard hospital meal (the same as given to group I), received an "all in one" type of total parenteral nutrition (TPN) for 5 days prior to surgical procedure. The mixture contained carbohydrates (glucose solutions), lipids (lipid emulsions) and amino acid solutions. Vitamins, 10% NaCl-20ml, 15% KCl-10ml, 20% $MgSO_4$-4ml and microelements were added to the TPN bag. Total energetic value was 10 kcal/kg of body weight. Group III (TPN + preOp), consisted of 25 patients who apart from standard hospital diet and parenteral nutrition (TPN with the same ingredients and energetic value as in group II), received, before the operation, oral preOp preparation, the components of which are shown in *Tab. 2*.

The preOp preparation was administered in doses according to the manufacturer's standard recommendations.

Table 1. **Demographic data presentation of particular clinical groups.**

Demographic data	Group I (NIL)	Group II (TPN)	Group III (TPN + preOp)
Age	65.6 (51 - 83)	65.4 (34 - 81)	67 (53 - 84)
Gender:			
Male (n / %)	13 (52 %)	13 (52%)	12 (48%)
Female (n / %)	12 (48 %)	12 (48%)	13 (52%)
Localization of cancer			
stomach n (%)	15 (60 %)	15 (60%)	15 (60 %)
large intestine n (%)	10 (40%)	10 (40%)	10 (407%)

Table 2. **Ingredients in 100 ml preOp.**

Energetic value	Kcal	215
Proteins	G	0
Energy (%)		0
Carbohydrates, including:	g	12.6
monosaccharides and disaccharides	g	2.1
lactose	g	0
polysaccharides	g	10
Energy (%)		100
Lipids	G	0
Energy (%)		0
Dietary fiber	G	-
Mineral components		
Na	Mg	50
K	Mg	122
Cl	Mg	6
Ca	Mg	6
P	Mg	1
Mg	Mg	1
Osmolarity	mOsmol/l	240

At the evening before the surgery, the patients were given 800 ml of the preOp preparation and again 400 ml on the actual day of the surgery (but no later than 2 hours prior the surgical procedure commencement).

The study was conducted according to the rules of *Good Clinical Practice* of the Declaration of Helsinki, and the protocol was approved by the Bioethical Board of Medical University of Bialystok (approval number: R-I-002/191/2009). All participants of the research were informed in detail about its aim and written informed consent was obtained. All the patients underwent surgical procedures according to a unified protocol. In case of stomach cancer, a complete stomach removal with a standard D2 lymphadenectomy and splenectomy was performed. In case of large intestine cancer, depending on the carcinoma location, a resection of a descending colon and sigmoid colon with mesocolon was performed. Also, regional lymphadenectomy was performed.

In order to evaluate the insulin resistance level, blood samples for the serum glucose and insulin concentration evaluation were collected four times from each patient. The blood samples were taken from veins. The blood was taken in a standard procedure to 2.6-ml plastic tubes without anticoagulant. Next, it was centrifuged for 10 minutes at 3800 r.p.m. The serum received by this method was used for further analysis performed with a Glucose set (single-factor, liquid test set; Abbott) for the glucose test and Architect Insulin (8K41; Abbott) for the insulin test.

The results were processed by HOMA2Calculator in order to mark a modified HOMA IR index. The HOMA IR>1 indicated the presence of resistance to insulin.

Statistical analysis

The study was planned as a prospective, cohort study with intervention. A 50% insulin resistance level reduction after the intervention (TPN or TPN + preOp), was anticipated. An 80% research power and a 5% probability of incorrect rejection of zero hypothesis were assumed. The assumed proportion for groups in which interventions were performed and for control group was 1:1. Calculated minimal number of patients included into the research amounted to 11 patients in each group. Had the alpha factor been taken into account, 25 patients constituted each group what gave 75 patients in final result. The calculations were performed by StatDirect 2.6.2 (Tidestone Formula One® software, Copyright© 1993-1998 Tidestone Technologies Inc). Statistical analysis of the results was performed using licensed software Statistica version 8.0 (StatSoft, Poland). The ranks of all data were compared by the Kruskal-Wallis test. To compare differences in results between the study groups and for subsequent markings the following tests were applied: post-hoc, Dwass-Steele and Critchlow-Flinger. The observed differences were considered statistically significant when $p<0.05$.

RESULTS

Insulin resistance before surgical procedure

First marking of insulin resistance factor revealed no statistically significant differences *(p>0.05)* between the groups. The average values of HOMA-IR factor in the study groups were quite similar. Their numerical value was lower than 1, what proves preoperative insulin resistance. In group I (NIL), the average value of HOMA-IR factor was 0.62, with a minimal value equal to 0.40 and maximal reaching 0.90. For group II (TPN), the average value of HOMA-IR factor was similar: 0.62 (with a minimal value equal to 0.20 and maximal: 0.90). Also, in group III (TPN + preOp), similar values were observed. The average value of HOMA-IR factor was 0.66, with a minimal value equal to 0.30 and maximal: 0.90 (*Fig. 1*).

Insulin resistance immediately after surgical procedure

Immediately after the operation, blood samples for glucose and insulin level analysis were collected from all groups of patients. The HOMA-IR factor was observed to be significantly exceeding 1 in all studied groups, clearly indicating the presence of perioperative insulin resistance. Similarly to the previous marking, this case study revealed no statistically significant differences either. In the NIL group, the average value of HOMA-IR factor was 1.75, with a minimal value equal to 0.50 and maximal reaching 3.70. In the TPN group, the average value of HOMA-IR factor was also distinctively higher than 1 and equaled 2.02. Its minimal value was 0.40 and maximal 6.10. The TPN + preOp group

was similar to the other groups. The average value of HOMA-IR factor was 2.75 (1.0-8.10). *Fig. 2* presents these results graphically.

Insulin resistance during first 6 postoperative hours

Six hours after the surgery, the first relevant differences in insulin resistance level in particular clinical groups were observed. A significant decrease of the HOMA-IR factor was observed in the TPN + preOp group, in which TPN and oral preOp preparation was applied *(p<0.05)*. It was below 1, which proves the regression of perioperative insulin resistance. Its average value was 0.86, minimal: 0.30 and maximal: 0.63. The HOMA-IR factor for the two other groups was also below 1, still proving the presence of perioperative insulin resistance. In the NIL group, the average value of HOMA-IR factor was 2.77, with a minimal value equal to 1.40 and maximal: 4.80. In the TPN group, the average value of HOMA-IR factor was 2.07, with a minimal value equal to 0.80 and maximal: 6.30.

A statistically significant difference was found between the TPN + preOp group and the two other study groups (NIL and TPN) *(p<0.05)*. In the NIL and TPN groups, no statistically relevant variations in the average value of the HOMA-IR factor, were observed *(Fig. 3)*.

Figure 2. **Insulin resistance immediately after surgical procedure.**

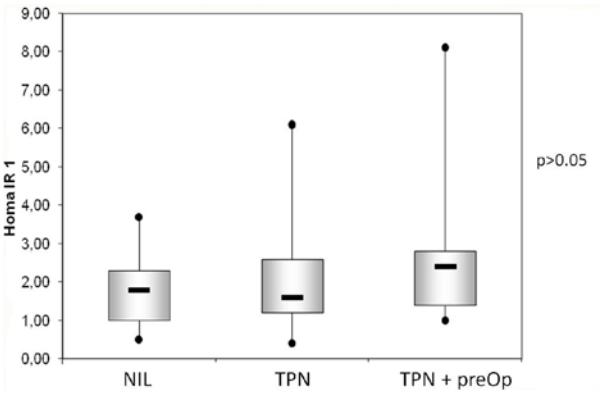
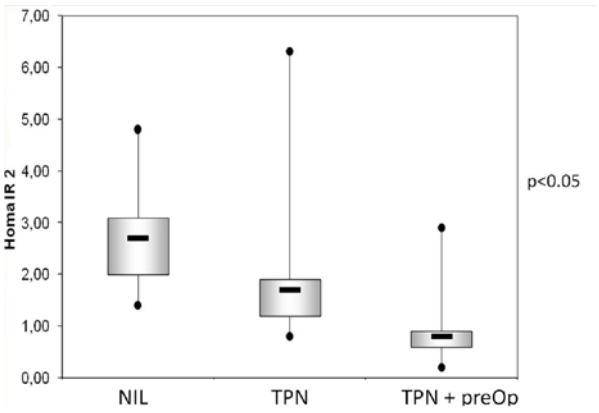


Figure 3. **Insulin resistance during first 6 postoperative hours.**



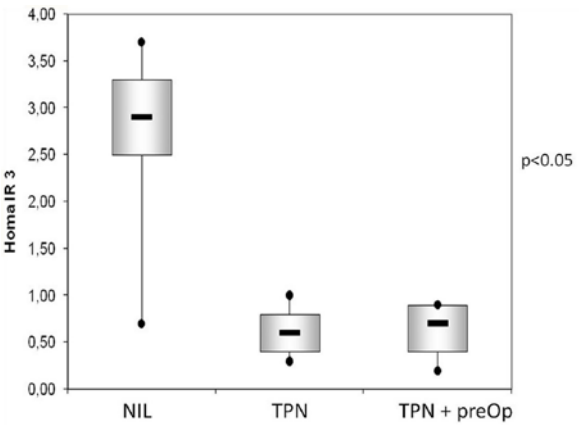
Insulin resistance 24 hours after operation

Another marking of insulin resistance level was performed 24 hours after the operation. As it was observed on the basis of these markings, the value of the HOMA-IR factor the TPN + preOp group was still below 1. Its average value was 0.63, minimal: 0.20 and maximum: 0.90. In the TPN group, the average value of HOMA-IR factor was also below 1 and its average value was 0.63. The minimal value in this group was 0.30 and maximal 1.0. Such values indicated the regression of perioperative insulin resistance in this group too. In the NIL group, the HOMA-IR factor exceeded 1 and its average value was 2.69 (0.70-3.70), which still supports the existence of insulin resistance. A statistically significant difference between groups TPN, TPN + preOp and group NIL *(p<0.05)*, was revealed. While comparing results in TPN and TPN + preOp groups, no statistically significant differences were noted *(Fig. 4)*.

DISCUSSION

The available literature indicates two major causes of perioperative insulin resistance and these are: surgical procedure as metabolic stress and preoperative fasting [4,5,7-19]. Until now, the researchers have been interested in the cases of patients in whom elective procedures of inguinal hernia, laparoscopic cholecystectomy, standard cholecystectomy, cheek correction or cardiosurgical procedures were performed [11-17]. The data on perioperative insulin resistance in patients with diagnosed cancers was not available. So far, in order to prevent insulin resistance syndrome, intravenous 20% glucose solutions were applied to elective surgical patients [9, 11, 14, 20-25]. The study by Ljungqvist *et al.* [11-14] shows approximately 50% effectiveness of this method. Few years later, a similar study was conducted during corrective procedure of cheeks [5,23,24]. In this case, intravenous glucose solution combined with insulin was applied. Patients treated with this therapy, showed no resistance to insulin, while in patients with no preoperative

Figure 4. **Insulin resistance 24 hours after operation.**



preparation, the resistance to insulin was still present for few postoperative days. Other studies, revealed positive influence of preoperative application of glucose solution with insulin in patients undergoing cardiosurgery [17]. Apart from the aforementioned effect of shortened time of significant insulin resistance, a decreased number of episodes of ischemic heart disease was observed [5, 17]. In order to prevent perioperative insulin resistance a combination of solutions consisting of glucose solution and lipid emulsions were also used.

Oral preparations which influenced the level of perioperative insulin resistance, were another method presented in 1995 [5]. At that time, commercially available oral liquids were used. This trial was unsuccessful due to properties of the applied substances (too long gastrointestinal passage). The next trial implied highly energetic drinks of low osmolarity for athletes [5, 15, 23]. The result was comparable to this noted while intravenous glucose solutions were applied. There are many other beneficial factors of oral preparations application. It is easier and less strenuous than intravenous. It eliminates the discomfort of thirst and hunger experienced before surgical procedure [5, 15, 22-25]. It is also highly important that this method is truly safe. The research conducted on 1000 patients showed not even a single complication due to drinking of the liquids within up to 2 hours prior to operation [5].

In the present study, conducted in our Clinic, a complete mixture designed for parenteral nutrition (group II) was applied. The mixture contained glucose, lipid and proteins solution. A total elimination of perioperative insulin resistance, as early as within first 24 postoperative hours, was noted in all patients in this group.

Even better results were obtained by combining total parenteral nutrition with the preOp oral preparation (group III). In this group a 100%-effective elimination of perioperative insulin resistance was observed after the sixth postoperative hour.

It should be also highlighted that, the patients underwent more extensive surgical procedures and their preoperative condition was worse due to the type of illness they suffered from. The issue of perioperative insulin resistance is still marginalized in everyday clinical practice. The so-far research aimed mainly at confirming the presence of the perioperative insulin resistance issue. However, as far as the perioperative insulin resistance prevention is concerned, it has been limited mostly to patients undergoing minor operations. This may be connected with the insulin resistance marking method itself. And this consequently was caused by lack of an easy and reliable method. The lack of prospective research on this issue, as well as, clinical implications with regard to it, are another reasons. The prospective clinical research presented in this study touches upon a rarely discussed issue of perioperative insulin resistance in surgical patients. Furthermore, based on this research, effective and useful clinical methods of perioperative insulin resistance prevention in surgical gastrointestinal carcinoma patients, have been presented.

CONCLUSIONS

On the basis of a prospective clinical research, we found that: standard oral nutrition in hospital conditions prior to surgical procedure causes significant increase of perioperative insulin resistance. Application of total parenteral nutrition (TPN) as an addition to oral nutrition in hospital conditions prior to surgical procedure leads to shortening of perioperative insulin resistance time. And finally, a combination of total parenteral nutrition (TPN) and oral application of carbohydrate preparations (preOp) before the operation is an effective and the best method of prevention and modification of perioperative insulin resistance phenomenon.

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