Perioperative glucose control in patients undergoing major thoracic surgical procedures – the role of anaesthesia and analgesia

Okołooperacyjna kontrola glikemii u pacjentów poddanych rozległym procedurom torakochirurgicznym – rola anestezji i analgezji

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Kardiochirurgia i Torakochirurgia Polska 2011; 8 (2): 244–250

Abstract

Background: The presence of hyperglycaemia during surgery and the perioperative period is associated with poor clinical outcomes, particularly in diabetic patients undergoing major surgical procedures. While the perioperative stress response may be managed by intensive insulin therapy, the choice of anaesthetic technique and pain control can also alleviate the metabolic response via its impact on the sympathetic system.
Aim: The aim of the study was to assess the impact of two types of anaesthesia and perioperative analgesia on glycaemic control in type 2 diabetic and non-diabetic patients undergoing major thoracic operations.
Material and methods: 80 patients, aged 57 ±9 years undergoing elective thoracic surgical procedures were enrolled in the study. Patients were divided into 4 groups: I – general and thoracic epidural anaesthesia (TEA), non-diabetic patients; II – total intravenous anaesthesia (TIVA), non-diabetic patients; III – general and TEA, patients with type 2 diabetes mellitus; IV – TIVA, patients with type 2 diabetes mellitus. Postoperative analgesia was provided by patient-controlled TEA with ropivacaine (groups I and III) or patient-controlled analgesia (PCA) with morphine (groups II and IV). An intensive insulin therapy protocol was implemented in all patients, aiming for a target glucose range of 80-110 mg/dl. Glycaemic values and insulin requirements during anaesthesia and three postoperative days were evaluated.
Results: No significant differences between the groups were found with respect to mean ±SD blood glucose levels or insulin requirements during anaesthesia. Postoperative glucose levels and insulin requirements were not different in studied patients and did not depend on analgesia type either.
Conclusion: The type of anaesthesia and postoperative analgesia has no influence on glycaemia and insulin requirements

Streszczenie

Wstęp: Śródoperacyjna i okołooperacyjna obecność hiperglikemii wiąże się z niekorzystnymi wynikami klinicznymi, szczególnie u pacjentów z cukrzycą poddawanych poważnym zabiegom chirurgicznym. Okołooperacyjną odpowiedź stresową można kontrolować intensywną insulinoterapią, a wybór techniki znieczulenia i kontroli bólu może również zmniejszyć odpowiedź metaboliczną poprzez wpływ na układ współczulny.
Cel: Celem pracy była ocena wpływu dwóch rodzajów śródoperacyjnego znieczulenia i analgezji na kontrolę glikemii u pacjentów z cukrzycą typu 2 i pacjentów bez cukrzycy, poddanych poważnym zabiegom torakochirurgicznym.
Materiał i metody: Do badania włączono 80 pacjentów w wieku 57 ±9 lat poddawanych zabiegom torakochirurgicznym. Pacjentów podzielono na 4 grupy: I – znieczulenie ogólne i zewnątrzoponowe piersiowe (ang. *thoracic epidural anaesthesia* – TEA), pacjenci bez cukrzycy; II – całkowite ogólne znieczulenie dożylne (ang. *total intravenous anaesthesia* – TIVA), pacjenci bez cukrzycy; III – znieczulenie ogólne i TEA, pacjenci z cukrzycą typu 2; IV – TIVA, pacjenci z cukrzycą typu 2. Analgezja pooperacyjna miała formę znieczulenia zewnątrzoponowego piersiowego sterowanego przez pacjenta z użyciem ropiwakainy (grupa I i III) lub analgezji sterowanej przez pacjenta (PCA) z użyciem morfiny (grupa II i IV). U wszystkich pacjentów zastosowano protokół intensywnej insulinoterapii w celu osiągnięcia poziomu glukozy rzędu 80–110 mg/dl. Dokonano oceny wartości glikemii oraz zapotrzebowania na insulinę podczas znieczulenia oraz przez trzy dni po zabiegu.
Wyniki: Nie wykazano żadnych znaczących różnic pomiędzy grupami w średnich ± odchylenie standardowe stężeniach glukozy we krwi czy w zapotrzebowaniu na insulinę podczas znieczulenia. Pooperacyjne stężenia glukozy oraz zapotrzebowanie

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in type 2 diabetic and non-diabetic patients undergoing major thoracic surgery.
Key words: perioperative stress, hyperglycaemia, analgesia.

na insulinę nie różniły się pomiędzy badanymi pacjentami ani też nie zależały od rodzaju analgezji.
Wnioski: Rodzaj znieczulenia oraz analgezji pooperacyjnej nie wpływa na glikemię i zapotrzebowanie na insulinę u pacjentów z cukrzycą typu 2 ani u pacjentów bez cukrzycy poddawanych poważnym zabiegom torakochirurgicznym.
Słowa kluczowe: stres okołooperacyjny, hiperglikemia, analgezja.

Introduction

The perioperative stress response leads to increased secretion of endogenous catecholamines, cortisol, glucagon, and growth hormone and disturbs the metabolism of carbohydrates. Glucose production increases and its peripheral utilisation is impaired – this is an effect of insulin deficiency and insulin resistance [1-3]. These changes are observed not only during the operation but also in the postoperative period and they are typical after major and long lasting procedures [1, 2, 4].

Gluconeogenesis has the most important role in perioperative metabolism of carbohydrates. It has been estimated to contribute ~90% to glucose production in that period. This is a consequence of perioperative fasting and the decrease in glucagon concentration [5]. Impaired hormonal glucose control leads to hyperglycaemia in surgical patients, including in those without preoperative disturbances in glucose metabolism [6].

Hyperglycaemia produces various deleterious effects; it inhibits immunological responses and healing of postoperative wounds by its impact on collagen production [7]. This is why in the perioperative period appropriate glucose control and insulin treatment must be implemented to prevent hyperglycaemic complications.

A study performed in 2001 by G. Van den Berghe et al. revealed that intensive insulin therapy with the objective to maintain plasma glucose between 80 and 110 mg/dl decreased morbidity and mortality in intensive care unit patients [8].

Since then the problem of normalisation of blood glucose has been intensively investigated also in patients after major surgical procedures. The positive role of intensive insulin therapy in the perioperative period was confirmed by the "Portland Project". Its authors, A.P. Furnary, Y.X. Wu, and S.O. Bookin, demonstrated a correlation between postoperative morbidity and mortality and blood glucose in diabetic patients undergoing cardiac operations [9, 10].

The type of anaesthesia may also reduce the perioperative stress response. Some studies describe the influence of different anaesthetic methods on metabolism of carbohydrates which are related to cardiac operations, but there are few studies determining the role of anaesthesia on glycaemic control in patients after major thoracic procedures. Particularly the role of thoracic epidural anaesthesia which is a gold standard for these operations is interesting and not well investigated.

Two different types of anaesthesia and perioperative analgesia for thoracotomy were compared in our study: general and thoracic epidural anaesthesia (TEA) and total intravenous anaesthesia (TIVA). The aim of the study was to assess the impact of these types of anaesthesia and perioperative analgesia on glycaemic control in type 2 diabetic and non-diabetic patients undergoing major thoracic surgical procedures using an original intensive insulin therapy protocol.

Material and methods

This was a prospective, randomised study performed on patients during and after anaesthesia for elective thoracotomy.

The study protocol was approved by a local Ethics Committee and informed consent was obtained from all subjects participating in the study. Patients were allocated to four groups; computer-guided randomisation was related to anaesthesia and analgesia type.

- group I – general and thoracic epidural anaesthesia (TEA), non-diabetic patients;
- group II – total intravenous anaesthesia (TIVA), non-diabetic patients;
- group III – general and TEA, patients with type 2 diabetes mellitus;
- group IV – TIVA, patients with type 2 diabetes mellitus.

Inclusion criteria:

- ASA (American Society of Anesthesiologists) II-III patients;
- type 2 diabetic patients treated with oral hypoglycaemic agents or non-diabetic patients respectively;
- patients > 18 years old (men and women);
- correct haemostatic parameters.

Exclusion criteria:

- lack of informed consent for participation in the study;
- abnormalities of coagulation;
- type 1 diabetic patients;
- *de novo* diabetes mellitus, poorly controlled diabetes mellitus, with at least one episode of hypoglycaemia during the past three months;
- liver or renal insufficiency;
- cardiac insufficiency with EF < 40%;
- endocrinological diseases: hyperthyroidism, hypothyroidism, adrenocortical insufficiency;
- BMI > 30 kg/m^2;
- inotropic support during or after operation;
- mechanical ventilation in postoperative period;
- reoperation up to the third day after surgery.

The preoperative investigations included spirometry and initial plasma blood glucose levels on the day of admission to hospital. The patients' demographic data are shown in Table I.

All patients were premedicated with oral midazolam (Dormicum, Roche, Switzerland) approximately one hour before surgery.

In groups I and III a thoracic epidural catheter (Epidural Catheter, Becton-Dickinson, USA) was inserted before surgery at the level of Th4-Th7. The dose test of 3 ml of 1% ropivacaine (Naropin 1%, AstraZeneca, UK) and an initial dose of 0.5% ropivacaine with 0.00075% fentanyl (Fentanyl, WZF Polfa, Poland) were administered before induction of general anaesthesia according to the protocol: 1 ml of mixture/segment + 0.1 ml/segment for each 5 cm of height under 150 cm.

Intraoperative analgesia in these groups was maintained with continuous epidural infusion of 0.5% ropivacaine with 0.00075% fentanyl according to the protocol: 0.8 ml of mixture/segment/hour + 0.05 ml/segment for each 5 cm of height under 150 cm.

In this way 8 thoracic segments were blocked. An arterial cannula and central venous catheter were inserted under local anaesthesia for continuous monitoring of arterial and central venous pressure during anaesthesia.

Patients in all groups received propofol (Diprivan 1%, AstraZeneca, UK) intravenously by infusion using the TCI (target controlled infusion) delivery system and the Base Primea (Fresenius Vial, France) pump. The effect-site propofol concentration was 2.5-4.5 µg/ml to provide accurate haemodynamic control and anaesthetic depth, which was monitored using the Bispectral Index (BIS A-2000 XP, Aspect Medical Systems, USA). Target bispectral index values were 40-60%.

2 mg/kg of cisatracurium (Nimbex, GlaxoSmithKline Pharmaceuticals S.A., GB) was given intravenously to facilitate tracheal intubation and during the procedure by infusion with a rate of 1.5 – 3 µg/kg/min. Muscular weakness was controlled with the TOF Guard (Organon Teknika, Belgium). TOF values were 0-1 (0-25%).

In groups II and IV remifentanil (Ultiva, GlaxoSmithKline Pharmaceuticals S.A., GB) was used intravenously as an analgesic agent with the Base Primea pump. The effect-site concentration of remifentanil was 4-6 ng/ml.

Endotracheal intubation was performed with a left double-lumen tube (Broncho-Cath, Mallinckrodt, Ireland). Its position was confirmed with a bronchofiberscope (Fibroskop FI – 9SB PENTAX, Varimed, Poland).

In all groups patients received 4-6 ml/kg/h of fluids (colloid to crystalloid ratio was 1 : 3). Additionally, 5% glucose infusion with a rate of 1.4 ml/kg/h was used to prevent hypoglycaemia. Haemodynamic parameters were registered before the induction and after tracheal intubation. When systolic blood pressure decreased during anaesthesia by more than 20% of initial values the target propofol concentration was reduced by 0.5 µg/ml. In the next step the effect-site concentration of remifentanil was decreased by 1 ng/ml and in epidural anaesthesia groups the local anaesthetic infusion rate was reduced by half the initial rate.

Standard haemodynamic and ventilatory parameters were monitored intraoperatively. Glycaemic control was performed using an Ascensia Entrust glucometer (Bayer, Germany) in the capillary blood before and after induction of anaesthesia and every 30 min during the procedure. Short acting insulin infusion (Gensulin, Bioton, Poland) was started when the glucose concentration was 110 mg/dl.

According to the intensive insulin therapy model, the target of intraoperative glycaemic control was set at 80-110 mg/dl and continuous infusion of insulin was performed with the protocol presented in Table I. When

Tab. I. Intraoperative intensive insulin protocol

5% glucose at a rate of 1.4 ml/kg/h
patient weight 50 kg – 70 ml/h 60 kg – 84 ml/h 70 kg – 100 ml/h 80 kg – 112 ml/h 90 kg – 126 ml/h
insulin (50 IU/50 ml) infusion rate: ≤ 110 mg/dl – STOP 110–120 mg/dl – 1 ml/h 120–150 mg/dl – 2 ml/h 150–170 mg/dl – 4 ml/h 170–200 mg/dl – 5 ml/h 200–250 mg/dl – bolus of 4 IU of insulin *i.v.* + infusion rate of 5 ml/h 250–300 mg/dl – bolus of 6 IU of insulin *i.v.* + infusion rate of 5 ml/h > 300 mg/dl individual management
glycaemic control every 30 min

Tab. II. Postoperative intensive insulin protocol

day 0–5% glucose at a rate of 0.7 ml/kg
patient weight 50 kg – 35 ml/h 60 kg – 42 ml/h 70 kg – 50 ml/h 80 kg – 56 ml/h 90 kg – 63 ml/h 1 day, STOP 5% glucose infusion
insulin (50 IU/50 ml) infusion rate: ≤ 110 mg/dl – STOP 110–120 mg/dl – 1 ml/h 120–130 mg/dl – 2 ml/h 130–150 mg/dl – 2.5 ml/h 150–160 mg/dl – 3 ml/h 160–170 mg/dl – 3.5 ml/h 170–200 mg/dl – 4 ml/h 200–220 mg/dl – bolus of 4 IU of insulin *i.v.* + infusion rate of 4 ml/h, glycaemic control hourly 220–250 mg/dl – bolus of 4 IU of insulin *i.v.* + infusion rate of 4.5 ml/h, glycaemic control hourly 250–300 mg/dl – bolus of 4 IU of insulin *i.v.* + infusion rate of 5 ml/h, glycaemic control hourly > 300 mg/dl individual management
glycaemic control every 4 hours

after the surgical procedure the blood glucose value was 110 mg/dl or more, intravenous insulin infusion was continued postoperatively using the protocol presented in Table II. Capillary blood glucose levels were measured every 4 hours or more frequently. Insulin delivery was accompanied with a 5% glucose infusion with a rate of 0.7 ml/kg/h.

The first meal was given to patients in the morning one day after surgery and 5% glucose infusion was stopped. Intravenous insulin infusion was continued according to glycaemia during three postoperative days (Table II) or until the removal of chest drains and discharge of the patient from the postoperative room.

Postoperative epidural analgesia in the first and third group was conducted with 0.2% ropivacaine and 0.0006% fentanyl with the patient-controlled epidural analgesia (PCEA) method. The basal PCEA infusion rate was 7 ml/h, bolus PCA was 3 ml and refractory time was 20 min. In other groups intravenous morphine infusion with the patient-controlled analgesia (PCA) system was used with a basal rate of 2 mg/h, bolus PCA of 2 mg and refractory time of 5 min. Efficacy of analgesia was evaluated by a numeric rating score (NRS) and the Prince Henry Hospital Pain Score (PHHPS) during Acute Pain Service visits.

Statistical analysis included demographic data, perioperative glycaemic values and insulin requirements. Numerical data are presented as mean and standard deviation. The data distribution was analysed using the Kolmogorov-Smirnov test. Depending on the result of this analysis, they were further analysed with an ANOVA test or Kruskal-Wallis test. Student's t-test or Mann-Whitney test was used for repeated measurements. Binary data are shown as the number and percentage and compared using the χ^2-test. $P < 0.05$ was considered significant.

Results

Eighty-six patients were included in the study and 80 finished it according to the protocol. In all groups the percentage of patients excluded from the study was comparable. Demographic data and perioperative parameters were similar between the groups, as shown in Table III.

The values of mean ±SD of capillary blood glucose during anaesthesia were: I 94.7 ±15.3 mg/dl vs. II – 95.0 ±18.5 mg/dl and III – 110.4 ±23.9 mg/dl vs. IV – 116.7 ±19.6 mg/dl and insignificant differences were found in patients without and with type 2 diabetes mellitus, as shown in Figure 1. The intra-group analysis indicated an important increase in blood glucose levels during anaesthesia in comparison to initial glucose values before induction (Fig. 1).

Intraoperative insulin requirements were not different between groups (I – 0.39 ±0.7 IU/h vs. II – 0.32 ±0.6 IU/h and III – 0.97 ± 1.2 IU/h vs. IV – 1.1 ±0.9 IU/h) and there was no influence of anaesthesia type (Fig. 2).

Postoperative data analysis demonstrated that there were no significant differences concerning mean ±SD of glycaemic values between groups I (105.9 ±10.2 mg/dl) and II (107.4 ±13.5 mg/dl; Fig. 3) and groups III (118.3 ±15.5 mg/dl) and IV (122.6 ±20.7 mg/dl; Fig. 3) during three postoperative days. Postoperative insulin requirements were also statistically comparable in different groups during three consecutive days (Fig. 4).

Tab. III. Demographic data and perioperative parameters

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	Group IV (n = 20)	I vs. II	II vs. IV	III vs. III	IV vs. IV	
age [years]	55	±6	52	±13	61	±9	59	±11	
height [cm]	172	±8	171	±8	167	±10	170	±9	
weight [kg]	72	±13	72	±15	73	±15	75	±16	
body mass index [kg/m^2]	24.4	±3.4	24.8	±4.9	26	±4	26	±5	
body surface area [m^2]	1.9	±0.2	1.9	±0.2	1.9	±0.2	1.9	±0.2	
male/female ratio	16/4		15/5		12/8		14/6		
ASA (II/III) ratio	16/4		12/8		11/9		13/7		p-value
coronary artery disease	1	(5%)	2	(10%)	3	(15%)	2	(10%)	NS
hypertension	5	(25%)	4	(20%)	10	(50%)	11	(55%)	
COPD	6	(30%)	2	(10%)	3	(15%)	4	(20%)	
smoking cigarettes	13	(65%)	11	(55%)	10	(50%)	9	(45%)	
FEV1 [%]	79.4	±14.3	87.7	±15.8	79.8	±16.1	85.1	±18.7	
FVC [%]	87.0	±12.2	95.5	±15.9	88.8	±15.7	92.8	±21.5	
FEV1/FVC [%]	89.1	±14.3	99.0	±11.1	89.7	±13.3	91.5	±17.2	
*glucose [mg/dl]	94	±19	95	±13	105	±21	108	±21	p-value NS

**Glucose on admission [mg/dl] – group I vs. II and group III vs. IV.*
Data are given as mean ± standard deviation or percentage. COPD – chronic obstructive pulmonary disease, FEV1 – forced expiratory volume in one second, FVC – forced vital capacity, FEV1/FVC – forced expiratory volume in one second and forced vital capacity ratio.

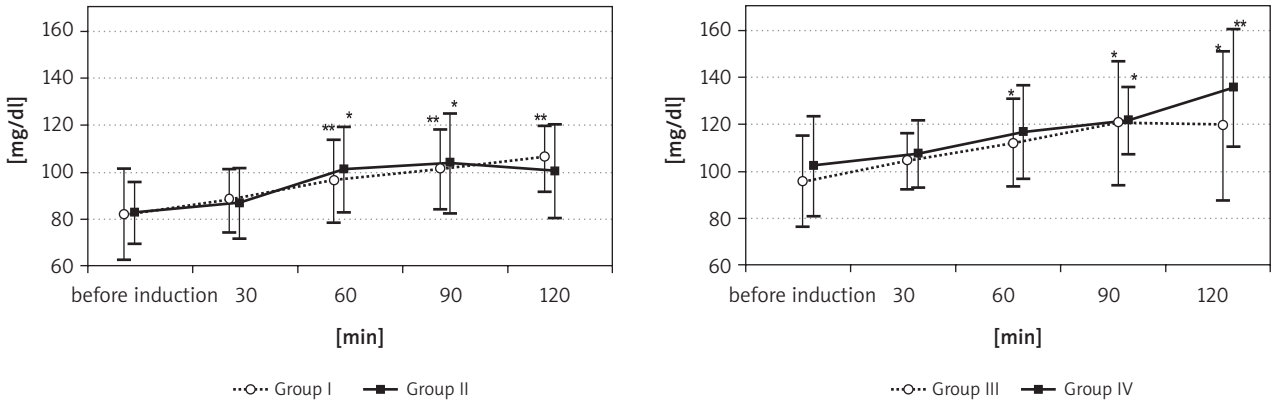

Fig. 1. Intraoperative glycaemia (mg/dl). Intra-group analysis (*p < 0.05, **p < 0.01 – significant differences from values observed before induction of anaesthesia)

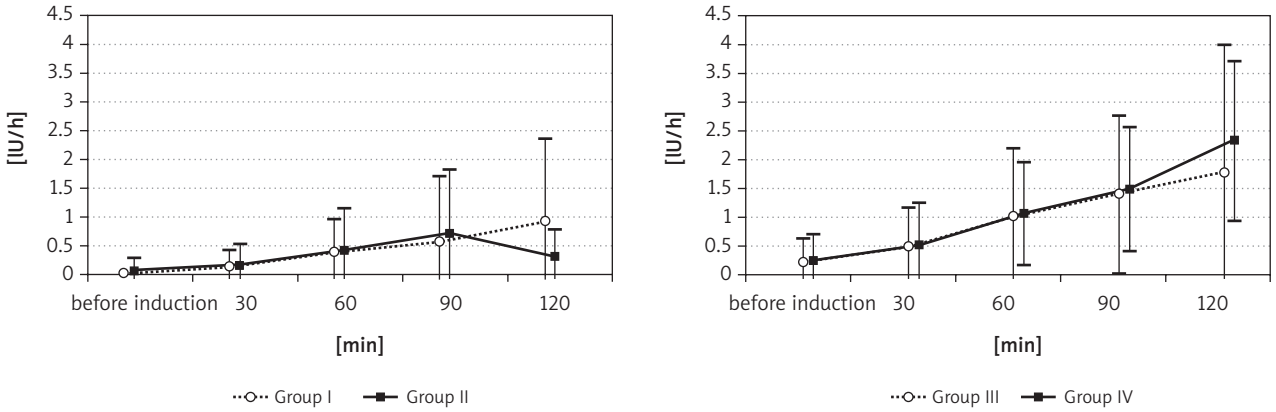

Fig. 2. Intraoperative insulin requirements (IU/h)

Discussion

The influence of two different types of anaesthesia and analgesia on perioperative glycaemic control were examined. Epidural anaesthesia is a recognised method of perioperative analgesia in thoracic surgery patients. Performed in the thoracic region of the spinal column it has a positive influence on haemodynamics during surgical procedures and decreases the risk of postoperative complications such as atelectasis, pneumonia, myocardial infarction, renal insufficiency, or stroke [11-13]. Combined with inhalational anaesthesia it ensures haemodynamic stability, effective perioperative analgesia and decreased opioid requirement [14, 15]. Also total intravenous anaesthesia effectively suppresses the haemodynamic stress response induced by surgical stimulus [16].

The metabolic response to epidural anaesthesia in comparison to other types of anaesthesia has been analysed in only a few publications and therefore needs further exploration [17, 18].

In our study we examined patients without diabetes and with type 2 diabetes mellitus treated by oral hypoglycaemic agents, which fulfilled good glycaemic control criteria. Patients with poorly controlled type 2 diabetes mellitus were qualified by an internist for subcutaneous insulin in the perioperative period and the operation was postponed. These patients did not participate in the study (exclusion criterion). Good preoperative glycaemic control was confirmed by mean glucose values before induction of anaesthesia, which were in the normal range. This may be a result of persistent activity of oral hypoglycaemic drugs.

The study of Cammu et al. [19] indicated that glycaemia before anaesthesia induction is a good predictor of insulin requirements in the perioperative period. In their study, glucose concentration before anaesthesia above 110 mg/dl pointed to difficulty in glycaemic control during and after the operation. Glycaemic values of 110 mg/dl or less were associated with a decrease in insulin requirements. In our study this threshold of mean glycaemia before induction was not exceeded, which may explain the good intraoperative glycaemic control and low insulin requirement.

The study demonstrated that the type of anaesthesia had no influence on either glycaemia or insulin requirements during the intraoperative period in patients with or without diabetes mellitus type 2. Therefore there is no superiority of epidural anaesthesia over total intravenous anaesthesia in the control of glycaemia.

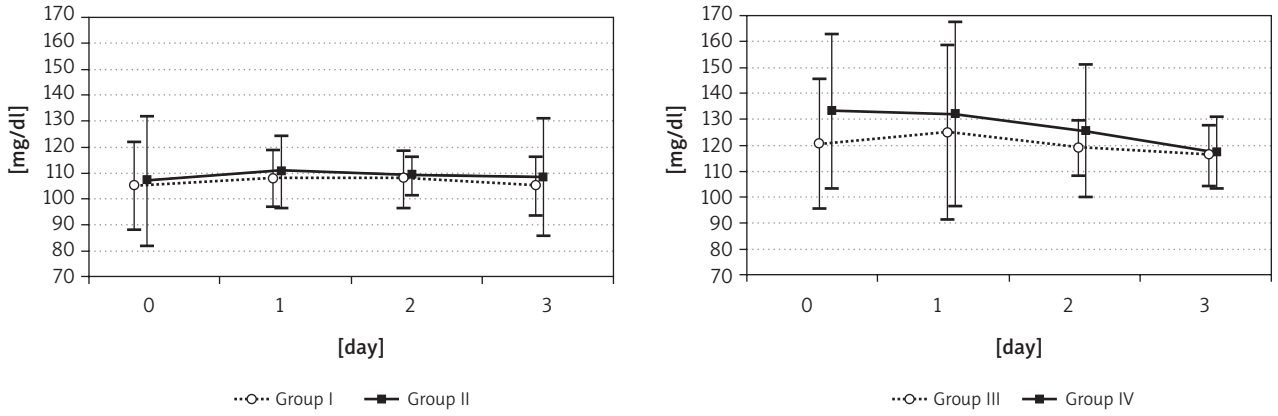

Fig. 3. Glucose values (mg/dl) in the postoperative period

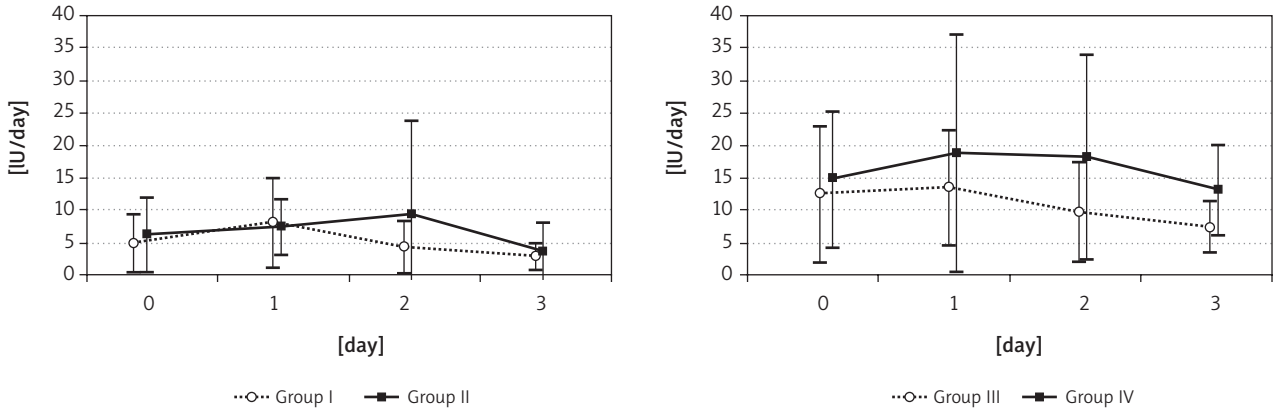

Fig. 4. Insulin requirements (IU/d) in the postoperative period

These observations were confirmed by Hennek et al. [20]. They demonstrated that combined general and epidural anaesthesia for pulmonary resections did not reduce intraoperative metabolic stress. Other authors [21] suggest that thoracic epidural anaesthesia improves glucose homeostasis but only during the 24-hour perioperative period in patients undergoing coronary artery bypass grafting procedures.

Intra-group statistical analysis of intraoperative glycaemia in our patients indicated the increase of glucose values in all investigated groups according to the anaesthesia time. Such a successive increase of glycaemia during the operation was confirmed in the study of Carvalho et al. [22], which could result in increased postoperative complications [23].

In our study the blood glucose target was 80-110 mg/dl. In most patients in the intraoperative period one or more blood glucose result was 110 mg/dl or more. Later they were treated by intravenous insulin infusion independently of the presence of diabetes. The glucose set target was also exceeded in fasting patients without diabetes, which confirms the theory of the influence of perioperative stress on glycaemic values.

It is difficult to assess the insulin requirement in the perioperative period because it is dependent on various factors such as blood glucose control before the operation, type and length of procedure, operative stress, weight of the patient and insulin resistance. In consequence, there is no universal protocol for insulin administration. This is reflected in a retrospective study of 350 patients from the bariatric department with type 2 diabetes who were administered continuous intravenous insulin therapy. The average insulin demand during surgery was 5.8 IU/h [24], which was almost twice as large as the values applied in our study. This may have resulted from insulin resistance in patients with high BMI. However, it should be noted that intravenous insulin administration allows lower insulin consumption compared with subcutaneous insulin administration, which is also connected with lower costs of treatment.

In our study the highest insulin requirement was observed at day 0 of surgery in the group of patients with type 2 diabetes undergoing anaesthesia with remifentanil. However, it was not statistically significant. We did not observe significant differences regarding glycaemia and insulin requirements depending on the applied anaesthesia in the following postoperative days. Thoracic epidural anaesthesia had no influence on blood glucose values despite many other disadvantages of this technique. Opinions of its impact on postoperative glycaemic values

are divided and the shortage of data in the literature prevents us from forming final conclusions. Anderson and colleagues [18] found that epidural anaesthesia improves glycaemic homeostasis only during the first 24 hours after surgery but does not lower hyperglycaemia within the next 3 days after coronary artery bypass surgery. A similar conclusion was expressed by Kilickan et al. [21] on the basis of the observation of different cardiac surgery patients.

Intensive insulin treatment in the intraoperative period has been introduced in only a few medical centres. Moreover, these methods are diverse in terms of defined target glycaemic values and do not require such strict glycaemic control as was adopted in the intensive care units.

A limitation of the study is connected with the inclusion of patients only with well-stabilized type 2 diabetes in the preoperative period. Inclusion in the study of all diabetic patients treated with oral hypoglycaemic agents and insulin would provide a better insight into the state of metabolic homeostasis of patients before thoracic surgery. Additionally, diabetic patients who are still not stabilised gain benefit from intensive insulin therapy.

Conclusions

Different methods of anaesthesia (i.e. general and thoracic epidural) and postoperative analgesia (i.e. epidural or i.v. PCA) did not influence glycaemic values or insulin demand in patients with type 2 diabetes and non-diabetic patients. Neither of the applied anaesthesiological techniques showed superiority in terms of metabolic stress relief. As a result, both methods of anaesthesia may be applied in patients undergoing thoracic surgery regardless of the occurrence of type 2 diabetes in the history of patients treated with hypoglycaemic agents.

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