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Effects of peri-operative administration of steroids on the blood glucose levels of patients with and without diabetes undergoing laparoscopic cholecystectomy

Laparoskopik kolesistektomide peroperatif uygulanan steroidin diyabetik ve diyabetik olmayan hastaların kan şekeri üzerine etkileri

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Abstract
Aim: To examine blood glucose levels in patients with and without diabetes undergoing laparoscopic cholecystectomy under general anesthesia following intravenous administration of 8 mg dexamethasone to minimize postoperative complications.
Methods: Hundred patients, 50 patients with diabetes and 50 without diabetes, who underwent laparoscopic cholecystectomy and met the inclusion criteria, were divided into 2 groups. After administration of 8 mg dexamethasone, blood glucose values were observed at the 30th and 120th min and compared between the groups.
Results: Increase in blood glucose levels at the 30- and 120-min marks were statistically significant relative to the pre-induction blood glucose levels ($p=0.002$ and $p<0.001$, respectively) in the non-diabetic group. On comparing blood glucose levels at the 30- and 120-min marks, a statistically significant increase was seen to have occurred over time ($p<0.001$).
Conclusion: Results of the current study showed that dexamethasone caused hyperglycemia in patients with and without diabetes the 12 h after surgery. We recommend that after administration of dexamethasone, tight monitoring of blood glucose levels should be considered.
Keywords: Blood Glucose, Diabetes, Steroid

Öz
Amaç: Genel anestezi altında laparoskopik kolesistektomi yapılan diyabetik ve diyabetik olmayan hastalara postoperatif dönemde oluşabilecek komplikasyonları önlemek amacıyla uygulanan 8 mg deksametazonun kan şekeri üzerine etkilerini gözlemlemek.
Yöntemler: Laparoskopik kolesitektomi planlanan, çalışmaya katılma kriterlerini karşılayan 100 hasta, 50 diyabetik olmayan ve 50 diyabetik hasta olmak üzere iki gruba ayrıldı. 8 mg deksametazon uygulanmasından sonra 30. ve 120. dk kan şekeri değerleri ölçüldü ve gruplar arasında karşılaştırıldı.
Bulgular: Diyabetik olmayan grupta kan şekerindeki 30. ve 120. dk değerlerindeki artış indüksiyon öncesi kan şekeri değerlerine göre istatistiksel olarak anlamlı idi ($p=0.002$ ve $p<0.001$). Kan şekeri seviyelerinin 30. ve 120. dk değerleri karşılaştırıldığında, zaman ilerledikçe istatistiksel olarak anlamlı bir artış olduğu tespit edildi ($p<0.001$).
Sonuç: Çalışmamızın sonuçlarına göre deksametazon diyabetik ve diyabetik olmayan hastalarda cerrahiden 12 saat sonra hiperglisemiye yol açmaktadır. Bu sebeple deksametazon uygulanmasından sonra kan şekerinin sıkı bir şekilde izlenmesi gerektiğini önermekteyiz.
Anahtar kelimeler: Kan şekeri, Diyabet, Steroid

Introduction

Diabetes is a chronic metabolic disease that requires continuous medical care. It is characterized by insulin deficiency or related defects that lead to incomplete metabolism of carbohydrates, fats, and proteins. The prevalence of diabetes mellitus (DM) is rising globally, with the number of patients with diabetes expected to increase to 366 million by 2030 [1]. Currently, there are 2.6 million patients with diabetes in Turkey, of which approximately 0.8 million were unaware of the disease [2].

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Regulation of blood glucose levels is a crucial issue in individuals undergoing surgical treatment as the associated stress can produce hyperglycemia in both patients with and without diabetes. Although no definite blood glucose values have been established thus far, it is clinically accepted that insulin treatment is necessary if the blood glucose levels rise above 180 mg/dl [3-5]. However, peri-operative hunger, long-acting insulin, or oral anti-diabetic drugs administered prior to surgery can cause hypoglycemia. Infections and myocardial infarctions are also common complications associated with DM, with the risk of infection during the postoperative period being dependent on the peri-operative blood glucose levels rather than the HbA1c values [6,7]. Specifically, the risk of postoperative infection increases by 30% with every 40 mg/dL increase in blood glucose levels during surgery [8].

The risk of hyperglycemia can be minimized by selecting minimally invasive surgical procedures and neuroaxial anesthesia, both of which are associated with less surgical stress [9-11]. During general anesthesia, volatile anesthetics may increase blood glucose levels by promoting hepatic glucose production [3].

Administration of glucocorticoids during the peri-operative period can reduce the inflammatory, hormonal, and immunological effects of surgical stress, and prevent complications such as postoperative nausea, vomiting, and laryngeal edema. Additionally, these corticosteroids can also reduce peripheral and hepatic insulin sensitivity by affecting the post-receptor mechanisms, and increase the blood glucose levels by promoting gluconeogenesis or, in other words, the production of glucose from amino acids and fats. This effect may impair blood glucose regulation in both patients with and without diabetes, and previous studies have shown that even low doses of corticosteroids can lead to hyperglycemia [12].

The current study examined blood glucose levels in patients with and without diabetes undergoing laparoscopic cholecystectomy under general anesthesia following intravenous administration of 8 mg dexamethasone to minimize postoperative complications.

Materials and methods

This prospective, case-control study was conducted at the Department of Anesthesiology, Haydarpasa Numune Education and Research Hospital, Istanbul, Turkey, between August 2015 and August 2016. Ethical approval was obtained from the research ethics committee of the Haydarpasa Numune Education and Research Hospital (approval No. HNEAH-KAEK 2014/KK/65); informed consent was obtained from all patients. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

This study included 110 patients (age: 18–70 years) who were scheduled to undergo laparoscopic cholecystectomy. Of these, 10 patients were excluded from the study as one patient with diabetes and 3 patients without diabetes required additional steroids and 3 patients with diabetes and 3 patients without diabetes required surgical treatment that exceeded 2 h in duration. The final sample thus consisted of 100 patients (50 patients with diabetes and 50 without diabetes).

The exclusion criteria included a history of undergoing radiotherapy or chemotherapy within the last 6 months, body mass index >40 kg/m^2, immunosupression, and surgical durations exceeding 2 h due to associated complications. Patients using inhaled corticosteroids were also ineligible for inclusion as were those > 18 years and pregnant women.

Patients who underwent laparoscopic cholecystectomy at the Haydarpasa Numune Training and Research Hospital and met the inclusion criteria were divided into 2 groups based on the presence or absence of DM. Patients were pre-medicated with 0.5 mg atropine sulfate and 10 mg diazepam 30 min prior to surgery, and were monitored throughout the procedure. The fingertip blood glucose values were also measured using strips at the same time.

In order to check the accuracy of the glucometer devices Accu-Check (Roche Diagnostics, Indianapolis, IN) which were calibrated regularly, the blood glucose values of the first patient with diabetes were measured in the laboratory and compared with the values observed on the devices. Similar studies have previously measured blood glucose levels using a glucometer [13].

In the current study, routine administration of 0.5–1 mcg/kg fentanyl, 2 mg/kg propofol, and 1 mg / kg vecuronium bromide was carried out. Additionally, 8 mg dexamethasone was also delivered intravenously to prevent postoperative nausea and vomiting. Anesthesia was induced by administering 1% sevoflurane, 0.05–0.5 mcg/kg/min remifentanil infusion and 50% O_2 / 50% air. Additionally, 0.9% isotonic NaCl solution was administered throughout the operation, and blood glucose levels were measured using a fingertip strip. The values observed at the 30th and 120th min after dexamethasone administration were compared between the diabetic and non-diabetic (ND) groups.

Statistical analysis

The data have been presented using descriptive statistical methods (frequency, percentage, mean, standard deviation), and the Kolmogorov-Smirnov distribution test was used to examine the distribution of the data. Pearson's Chi-square test and Fisher's Exact test were used to compare categorical variables, and a t-test was used to compare parameters between groups. Repeat measurements of ANOVA were used for intra-group comparisons, and the level of statistical significance was set at p-value <0.05. All statistical analyses were performed using a statistical package, SPSS 21.0.

Results

This study included 100 patients, of which 50 were diagnosed with DM and 50 were without diabetes. Twelve (24.0%) of the patients in the DM group managed their diagnosis using exercise and diet, 30 (60.0%) patients used OAD, and 8 (16.0%) patients used insulin.

The mean age of patients in the DM group was significantly higher (p=0.004) than that of patients in the ND group. No significant differences in weight, height, gender, BMI (body mass index), and duration of surgery were observed between the DM and ND groups (p>0.05).

The pre-induction blood glucose, 30-min blood glucose, and 120-min blood glucose levels were significantly higher in the DM group (p<0.001). The increase in blood glucose levels at the 30 min mark was not statistically significant relative to the pre-induction blood glucose levels (p=0.287) in this group. However, the increase observed at the 120-min mark was statistically significant relative to the pre-induction blood glucose levels (p<0.001). Moreover, upon comparing the blood glucose levels at the 30- and 120-min marks, a statistically significant increase was seen to have occurred over time (p<0.001).

In the ND group, the increase in blood glucose levels at the 30- and 120-min marks were seen to be statistically significant relative to the pre-induction blood glucose levels (p=0.002 and p<0.001, respectively). Moreover, upon comparing the blood glucose levels at the 30- and 120-min marks, a statistically significant increase was seen to have occurred over time (p<0.001) (Table 1).

Table 1: Binary Pairwise Comparison of Data

Group	(I) measurement	(J) measurement	Mean Difference (I-J)	Std. Error	p	95% Confidence Interval of Difference [1] Lower	Upper
DM	1	2	−6.940	4.083	0.287	−17.062	3.182
		3	−34.860*	5.836	<0.001	−49.327	−20.393
	2	1	6.940	4.083	0.287	−3.182	17.062
		3	−27.920*	5.043	<0.001	−40.421	−15.419
	3	1	34.860*	5.836	<0.001	20.393	49.327
		2	27.920*	5.043	<0.001	15.419	40.421
ND	1	2	−10.380*	2.889	0.002	−17.541	−3.219
		3	−32.280*	4.720	<0.001	−43.981	−20.579
	2	1	10.380*	2.889	0.002	3.219	17.541
		3	−21.900*	4.456	<0.001	−32.946	−10.854
	3	1	32.280*	4.720	<0.001	20.579	43.981
		2	21.900*	4.456	<0.001	10.854	32.946

DM: Diabetes mellitus, ND: non-diabetic, * indicates p<0.05 and a statistically significant difference between the mean values, [1] Bonferroni multiple comparison test was used.
I and J represent the variable coding assigned by SPSS for the comparison of measurements. The differences between these codings and the mean values of the measurements were determined
1 = pre-induction blood glucose level
2 = blood glucose level at 30 min
3 = blood glucose level at 120 min

Discussion

Surgical stress is known to induce insulin resistance and hyperglycemia in patients with and without diabetes by triggering the secretion of hormones such as the growth factor hormone, glucagon, catecholamine and glucocorticoids. Hyperglycemia is induced within the first hour of surgery, and is seen to persist until the fifth postoperative day, proportionate to the magnitude of the surgical stress.

Glucocorticoids can be used to reduce the inflammatory, hormonal, and immunological effects of surgical stress in the peri-operative period [14]. Preoperative intravenous dexamethasone reduces postoperative inflammation and its associated laryngeal edema [15]. Dexamethasone also prevents postoperative nausea and vomiting [12]. A previous randomized, controlled, double-blinded study conducted by Thue Bisgaard et al. [16] included administration of either 8 mg dexamethasone or a placebo 90 min prior to laparoscopic cholecystectomy treatment. The patients were followed up with for 2 days postoperatively, and the pain, infection, vomiting and respiratory functions scores were recorded. Comparison of the 2 groups exhibited a reduction in these parameters, and the authors suggested that this could be attributed to the anti-inflammatory and immunosuppressive effects of dexamethasone.

Peri-operative steroids have both positive and negative effects, and the most significant adverse effect that may increase the risk of mortality and morbidity is that it increases hyperglycemic activity, even at low doses. Hans et al. [12] measured the blood glucose levels following administration of 10 mg dexamethasone to prevent postoperative nausea and vomiting following abdominal operations in 32 patients without diabetes and 31 patients with diabetes. The blood glucose values were seen to increase in both groups. Moreover, the blood glucose levels peaked at 120 min after dexamethasone administration in both groups, and the rate of elevation of blood glucose was also similar between the groups. These results demonstrated that even doses as low as 8 mg could induce significant elevations in blood glucose levels [12].

Given that surgical stress causes hyperglycemia and steroids administered for various reasons can contribute to this hyperglycemic effect further, peri-operative monitoring of patients with diabetes is essential as the risk of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome is increased. Delay in wound healing due to hyperglycemia, cerebral ischemia, renal ischemia, endothelial dysfunction, or wound infection may also occur.

These complications can directly affect the risk of postoperative mortality and morbidity, thus leading us to question exactly how much influence peri-operative administration of steroids had on the blood glucose levels of patients with and without diabetes. This study included patients undergoing laparoscopic cholecystectomy instead of open cholecystectomy [9,17] in order to minimize and standardize the effects of surgical stress on blood glucose levels.

Glucocorticoids were administered at various doses (8 mg, 10 mg, and 16 mg) to prevent postoperative nausea and vomiting, and no significant differences in the antiemetic effects were observed. Administration of 8 mg dexamethasone during induction was preferred as this was believed to be the minimum effective dose associated with the least side-effects.

A similar study conducted by Basem et al. [13] examined the effects of low doses of steroids on the blood glucose levels of surgically stressed patients with and without diabetes (n = 185). The authors proposed 2 hypotheses, as follows: a) patients with diabetes were more likely to exhibit an increase in blood glucose levels than those without diabetes, and b) steroid injections would lead to higher blood glucose levels in patients with diabetes than in those without diabetes. Dexamethasone (8 mg) and placebos were administered pre-surgically in 90 and 95 patients, respectively. The results of this study showed that patients with diabetes exhibited higher preoperative blood glucose levels than those without diabetes, and both groups presented with significantly elevated blood glucose levels during the operation. However, patients without diabetes exhibited a significant elevation of blood glucose levels following steroid injection, and this was in contrast to the patients with diabetes whose blood glucose levels were not significantly elevated after steroid injection.

Lunkins et al. [18] included 34 patients without diabetes undergoing craniotomy in their study. Of these, one group of patients received placebos only, one group received preoperative dexamethasone, one group received 10 mg of intravenous dexamethasone, and one group of patients received 4 mg of intravenous dexamethasone 6 h after surgery. All of the patients exhibited an increase in blood glucose levels for a period of 12 h. The highest increase in blood glucose levels was observed within the first 8–10 h in patients that had received intraoperative dexamethasone.

In our study, although the increase in blood glucose levels observed in patients without diabetes 30 min after induction was statistically significant, measured values were clinically acceptable in both groups (mean value: DM group = 135.6 mg/dl; ND group = 111.14 mg/dL). The increase in blood glucose level 120 min after induction was clinically significant in both patients with and without diabetes. Moreover, the peak blood glucose level was 265 mg/dl in the DM group and 275 mg/dl in the ND group.

Pasternak at al. examined the effects of 10 mg of dexamethasone administered to prevent cerebral edema in patients undergoing craniotomy, and found that the mean blood glucose levels were significantly higher in patients who had received dexamethasone than in those who had received the placebo [19].

The findings of these studies were in agreement with those of the current one, which also observed a clinically significant increase in mean blood glucose levels following glucocorticoid administration.

The study is limited by the fact that all the patients received 8 mg dexamethasone. The effect of dexamethasone should be assessed in comparison with patients who received placebo.

Dexamethasone has anti-inflammatory properties that prevent the adverse effects of surgical stress, affect post-receptor mechanisms, and cause hyperglycemia by reducing peripheral and hepatic insulin sensitivity. In agreement with this, the results of the current study showed that dexamethasone caused hyperglycemia in both patients with and without diabetes in the 12 h after surgery. We recommend that after administration of dexamethasone, tight monitoring of blood glucose levels should be considered.

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