Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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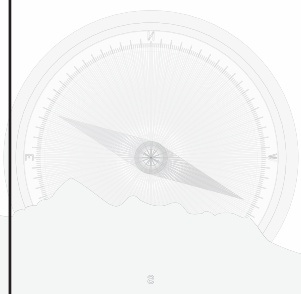

Abstract

Background: Perioperative hyperglycaemia is associated with postoperative complications after major surgery. However, more than 50% of surgical procedures are performed in an ambulatory setting, where glucose is not routinely measured. The objectives of this study were to investigate the change in capillary glucose during ambulatory surgery, to identify patients at risk for perioperative increasing glucose and to evaluate whether hyperglycaemia predisposes for complications after ambulatory surgery.

Methods: In this prospective multicentre cohort study, adult patients planned for ambulatory surgery, were included and capillary glucose was measured 1 hour before and 1 hour after surgery. Patients were contacted 90 days after surgery to determine the occurrence of postoperative complications.

Results: Nine hundred and nine patients were included, 48 (5.3%) patients had diabetes mellitus (DM). Overall median glucose increased from 5.4 mmol l^{-1} preoperatively to 5.6 mmol l^{-1} postoperatively ($p<0.001$). Hyperglycaemia, defined as plasma glucose ≥7.8 mmol l^{-1}, occurred in 8.8% of the patients. Dexamethasone administration (given in 406 [44.7%] patients) was a risk factor for glucose increase ($p<0.001$). Hyperglycaemia was not a risk factor for postoperative complications (OR 1.19, 95%CI 0.57-2.48, p=0.646). However, pre-diagnosed DM was a risk factor for postoperative complications, independent of hyperglycaemia (OR 2.56, 95%CI 1.10-5.97, P=0.030).

Conclusion: Minor ambulatory surgery is not associated with a clinically relevant increase in glucose. The very small glucose increase we observed could be attributed to the administration of dexamethasone for Post Operative Nausea and Vomiting (PONV) prophylaxis. Hyperglycaemia during ambulatory surgery is not associated with complications after discharge.

Introduction

In-hospital hyperglycaemia occurs frequently, both in patients with and without diagnosed diabetes mellitus (DM). Often, hyperglycaemia during hospital admission resolves spontaneously after hospital discharge and is referred to as "stress hyperglycaemia"(1). However, 15-46% of these patients have undiagnosed DM (1,2).

In several types of major surgery, such as pancreatoduodenectomy, liver transplantation and cardiac surgery, perioperative hyperglycaemia is associated with postoperative complications (3-5). However, the majority of surgical patients undergo minor surgery and are operated on in an ambulatory setting (6,7) Glucose is not routinely measured in patients without DM undergoing ambulatory surgery (8), thus hyperglycaemia due to stress or undiagnosed DM is easily missed.

Although patients undergoing ambulatory surgery are the largest surgical population at risk for stress hyperglycaemia, information on the incidence and clinical consequences of hyperglycaemia during ambulatory surgery is scarce. If we were to know the incidence of hyperglycaemia during ambulatory surgery and whether this is associated with postoperative complications, the efficacy and cost effectiveness of glucose control during ambulatory surgery can be assessed.

Therefore, the objectives of this study were to investigate capillary glucose change during ambulatory surgery in patients with and without DM, to identify patients at risk for perioperative increasing glucose and to evaluate whether hyperglycaemia predisposes for complications after ambulatory surgery.

Materials and methods

The study protocol NL37311.018.11 was approved by the Medical Ethical Committee of the Academic Medical Centre and the local ethical committee of the Diakonessenhuis. We included patients between October 1st 2011 and July 31st 2012. Written informed consent was obtained from every patient. This prospective multicentre observational cohort study was conducted in the ambulatory surgery departments of two hospitals (Academic Medical Centre (AMC), Amsterdam and Diakonessenhuis Zeist and Utrecht, The Netherlands). The AMC is an academic centre with a separate ambulatory surgery department, where predominantly orthopaedic and minor general surgery procedures are performed. The Diakonessenhuis is a non-academic centre where ambulatory surgery is predominantly focused on orthopaedic and laparoscopic inguinal hernia repair procedures. Reporting was done according to the STROBE-guideline.

Patients and study outline

Patients older than 18 years of age scheduled for ambulatory surgery with or without a history of DM were included. Both patients with DM type 1 and type 2 were eligible. After written informed consent, a capillary glucose sample was taken one hour before and one hour after surgery via finger stick. Capillary glucose was measured using the Accu-Chek Inform (Roche Diagnostics, Indianapolis, IN, USA). The Accu-Chek Inform is frequently used in studies as well as in clinical settings, with only 2.5% of inaccurate readings according to the International Organization for Standardization (ISO) criteria when used in a non-ICU setting (9). The time since last carbohydrate intake was recorded. Patients without DM and preoperative glucose ≥7.8 mmol l^{-1} were advised to see their general practitioner postoperatively. Patients with DM had to withhold insulin and glucose lowering tablets on the morning of surgery. In patients with DM, glucose >10 mmol l^{-1} was treated at the discretion of the attending anaesthesiologist (e.g. a bolus of intravenous short acting insulin), according to the local guidelines of each hospital. Patients without DM were not treated for hyperglycaemia.

Before surgery a brief questionnaire was completed, focused on patient characteristics and history of DM. Patients received dexamethasone for prophylaxis of nausea and vomiting at the discretion of the attending anaesthesiologist. No additional sources of glucose were administered during the perioperative period, and saline was used to dilute drugs. All details about the anaesthetic regime and the type of surgery were noted. We determined the occurrence of postoperative complications for the first 90 days after surgery. Therefore, we reviewed patients charts where available and all patients were contacted >90 days postoperatively for a short questionnaire by telephone. Patients were called on three different dates and times before they were considered as lost to follow-up.

Outcome measures

The primary outcome was median glucose change during ambulatory surgery as compared to preoperative fasting glucose. We identified risk factors for perioperative increase in glucose. Also the association of hyperglycaemia during ambulatory surgery and postoperative complications was assessed. Postoperative complications were defined as: death, hospital readmission, postoperative infection (e.g. wound infection, pulmonary infection or cystitis/urinary tract infection), wound bleeding, delirium, thromboembolic complications (e.g. myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism) and other complications. Postoperative infection was scored for events ranging from redness of the skin for which medical help was sought to antibiotic treatment for a postoperative fever with suspected infection. Prophylactic antibiotic treatment was not scored as a postoperative infection.

As secondary outcome measures the proportion of patients with hyperglycaemia (glucose ≥7.8 mmol l^{-1}) preoperatively, new postoperatively and during admission were calculated. The risk factors for pre- and new postoperative hyperglycaemia were assessed. Additionally the risk factors for postoperative complications were determined. The used cut-off value for hyperglycaemia was 7.8 mmol l^{-1} (140 mg dl^{-1}). This is in agreement with a recently performed trial, which showed that complications occurred more frequently above a glucose of 7.8 mmol l^{-1} and with the American Diabetes Association (ADA) cut-off value for DM during an oral glucose tolerance test (3,10).

Statistical analysis

No data about glucose change during ambulatory surgery was available, thus a formal power analysis was not possible. To ensure adequate power of the predictive model for the risk factors for hyperglycaemia, we aimed for the inclusion of 1000 patients.

Glucose change during surgery was analysed using the Wilcoxon signed-rank test and glucose change between subgroups (no DM without dexamethasone, no DM with dexamethasone, DM without dexamethasone and DM with dexamethasone) was analysed using the Mann Whitney-U test. The overall glucose change was calculated by subtracting the preoperative glucose value from the postoperative glucose value. A multivariate linear regression analysis was performed to identify risk factors for perioperative increase in glucose. The difference in complication rate between patients with and without hyperglycaemia during ambulatory surgery was calculated with the Chi-square test. The odds ratios (ORs) for risk factors for preoperative hyperglycaemia, new postoperative hyperglycaemia and hyperglycaemia at any time during admission were calculated with multivariate logistic regression analyses. In addition the ORs for risk factors of postoperative complications for the whole study population were calculated. In all regression analyses we adjusted for age, sex, BMI, ASA classification, dexamethasone use, DM and duration of surgery (divided in quartiles). Also, postoperative glucose was analysed by quartiles, to assess if the higher quartiles were associated with complications when compared to the lowest quartile. Statistical analyses were done using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population

One thousand five hundred twenty-nine patients were eligible for this study, of which 951 patients gave written informed consent. Four patients were excluded due to cancellation of surgery or conversion to local anaesthesia and one patient withdrew informed consent. One patient was excluded from the study because he received 30 mg pred-

nisolone per day for 5 days due to COPD GOLD classification II. Thirty-six patients were excluded because only one glucose measurement was available, leaving 909 patients for final analyses.

The patient characteristics are displayed in Table 1. With regard to patients with DM, in 43 patients their glucose was measured before and after surgery, but no additional insulin was administered; In three patients, a glucose-insulin infusion was started during surgery; In two patients, their own subcutaneous insulin pump was continued during surgery.

Table 1. Patient characteristics (n=909)

Male, n (%)	**465 (51.2)**
Mean age (years)	47.2 (15.3)
Mean body mass index (BMI)	25.9 (4.7)
Diabetes Mellitus, n (%)	48 (5.3)
Type 1	7 (0.7)
Type 2 treated with diet	1 (0.1)
Type 2 treated with tablets	31 (3.4)
Type 2 insulin dependent	9 (1.0)
Dexamethasone, n (%)	406 (44.7)
Intake of carbohydrate containing liquids < 2 h before surgery, n (%)	7 (0.8)
ASA-classification, n (%)	
ASA 1	533 (58.6)
ASA 2	357 (39.3)
ASA 3	19 (2.1)
Type of anaesthesia, n (%)	
General anaesthesia	668 (73.5)
Spinal anaesthesia	178 (19.6)
Peripheral nerve block	63 (6.9)
Median duration of surgery (min)	28 (28 [18-46])
Treating specialty, n (%)	
Orthopaedics	307 (33.8)
General surgery	273 (30)
Gynaecology	82 (9)
Urology	20 (2.2)
ENT-surgery	74 (8.1)
Neurosurgery	4 (0.4)
Plastic surgery	69 (7.6)
Radiotherapy	13 (1.4)
Ophthalmology	47 (5.2)
Maxillofacial surgery	19 (2.1)

Values are mean (SD), median (IQR) or number (proportion). (ASA) American Society of Anaesthesiologists, (ENT) ear-nose-throat

Follow up was completed for 670 patients (73.7%), of whom 40 had known DM (6.1%). The remaining patients could not be contacted. Any of the predefined complications occurred in 15.8% of patients. The main postoperative complication was postoperative infection (8.1%, Table 2).

Table 2. Postoperative complications

	All (n=670)	Normal range (n=597)	Hyperglycaemia (n=73)
Any complication	**106 (15.8)**	**87 (14.6)**	**19 (26.0)***
Death	0 (0.0)	0 (0.0)	0 (0.0)
Re-admission	27 (4.0)	20 (3.4)	7 (9.6)*
Wound bleeding	25 (3.7)	24 (4.0)	1 (1.4)
Postoperative infection	54 (8.1)	46 (7.7)	8 (11.0)
Postoperative delirium	11 (1.6)	7 (1.2)	4 (5.5)*
Thrombo-embolic complications	5 (0.7)	5 (0.8)	0 (0.0)
Other	9 (1.4)	7 (1.2)	2 (2.8)

Values are n (%). * Chi square test $p<0.05$

Perioperative glucose values and hyperglycaemia

Overall median glucose increased from 5.4 (IQR 5.1-5.9) preoperatively to 5.6 mmol l^{-1} (IQR 5.1-6.4) postoperatively ($p<0.001$). In the subgroup of patients with DM, glucose changed from 8.0 (IQR 6.4-10.1) to 8.2 mmol l^{-1} (IQR 6.3-9.7, $p=0.123$). Although patients with DM had higher glucose values compared to patients without DM, the increase in glucose in patients with known DM was not statistically significant. A total of 80 (8.8%) patients had hyperglycaemia (glucose ≥7.8 mmol l^{-1}) at any time during admission (Table 3), while 49 (5.7%) had no previous diagnosis of DM. Two patients were subsequently diagnosed with DM; one patient with DM type 1 and one patient with DM type 2. Fourty (4.4%) patients developed hyperglycaemia during surgery.

Table 3. Hyperglycaemia during admission in patients with and without diabetes

	All (n=909)	Non DM (n=861)*	DM (n=48)
Preoperative hyperglycaemia	40 (4.4)	13 (1.5)	27 (56.3)
Postoperative hyperglycaemia	65 (7.2)	40 (4.6)	25 (52.1)
New postoperative hyperglycaemia	40 (4.4)	36 (4.2)	4 (8.3)
Hyperglycaemia during admission	80 (8.8)	49 (5.7)	31 (64.6)

Values are n(%). *(DM) Diabetes mellitus.

In total, 398 patients without DM received a single dose of dexamethasone at a mean dosage of 4.2 mg (SD 2.0) during surgery. In these patients, glucose significantly

increased from 5.4 mmol l^{-1} (IQR 5.1-5.9) preoperatively to 5.8 mmol l^{-1} (IQR 5.3-6.5) postoperatively (p<0.001). In patients without DM, who did not receive dexamethasone, median glucose slightly decreased from 5.4 mmol l^{-1} pre- to 5.3 mmol l^{-1} postoperatively (p=0.052, Table 4).

Table 4. Median glucose values pre- and postoperative in patients with and without diabetes

	All (n=909)	Non DM (n= 861)		DM (n=48)	
		No Dexa (n=461)	Dexa (n=398)	No Dexa (n=40)	Dexa (n= 8)
Preoperative	5.4 (5.1 – 6.0)	5.4 (5.0 – 5.9)	5.4 (5.1 – 5.9)	8.5 (6.7 – 11.0)	6.6 (5.7 – 9.3)
Postoperative	5.6 (5.1 – 6.4)	5.3 (4.8 – 6.0)	5.8 (5.3 – 6.5)	8.1 (5.9 –9.7)	8.3 (7.0 – 9.5)
WSR – test	*p<0.001*	*p=0.262*	*p<0.001*	*p=0.006*	*p=0.093*
Median difference	0.2 (-0.3 – 0.6)	-0.1 (-0.5 – 0.4)	0.4 (0.0 – 0.9)	-0.3 (-1.8 – 0.3)	1.5 (0.3 – 2.6)
MWU – test	*n/a*	*p<0.001*		*p=0.002*	

Values are median (IQR) stated in mmol l^{-1}. (DM) diabetes mellitus. (Dexa) dexamethasone, (WSR-test) Wilcoxon signed rank test. (MWU) Mann Whitney-U.

Factors associated with an increase in glucose during ambulatory surgery were administration of dexamethasone (β 0.53, 95% CI 0.40-0.65, p<0.001) and duration of surgery (β 0.13, 95%CI 0.07- 0.18, p<0.001), adjusted for age, sex, BMI, ASA classification and DM.

In the logistic regression analysis, DM was a risk factor for hyperglycaemia at any time during admission (OR 26.81, 95% CI 11.08-64.89, p<0.001), after adjustment for age, sex, BMI, ASA classification, dexamethasone use and duration of surgery. DM was also the only risk factor for preoperative hyperglycaemia (OR 53.29, 95%CI 21.44-132.48, p<0.001) when adjusted for age, sex, BMI and ASA classification. Dexamethasone was a risk factor for new postoperative hyperglycaemia (OR 3.96, 95% CI 1.80-8.68, p=0.001), when adjusted for age, sex, BMI, ASA classification, DM and duration of surgery. Also, age (OR 1.06, 95% CI 1.03-1.09, p<0.001), BMI (OR 1.11, 95% CI 1.03-1.19, p=0.004) and duration of surgery (3rd quartile >28 min, OR 9.46, 95% CI 1.15-78.18, p=0.037 and 4th quartile >46 min, OR 29.21, 95% CI 3.88-223.99, p=0.001) were associated with new postoperative hyperglycaemia.

Glucose and postoperative complications

The incidence of postoperative complications was 26% in the patients with hyperglycaemia and 14.6% in the patients without hyperglycaemia (p=0.012, Table 2). In the logistic regression analyses, perioperative increase in glucose was not a risk factor for postoperative complications (OR 1.07, 95% CI 0.88-1.32, p=0.498) when adjusted for age, sex, BMI, ASA classification, DM, dexamethasone use and duration of surgery. Also, neither hyperglycaemia at any time during admission (OR 1.19, 95% CI 0.57-2.48,

p=0.646, Figure 1), nor new postoperative hyperglycaemia (OR 0.96, 95% CI 0.37-2.50, p=0.930) were associated with postoperative complications. Furthermore, the upper three quartiles of postoperative glucose (glucose >5.1; >5.6 and >6.4 mmol l^{-1}) were not associated with postoperative complications, when compared to the lowest quartile (glucose <5.1 mmol l^{-1}, p=0.679, p=0.465 and p=0.958, respectively).

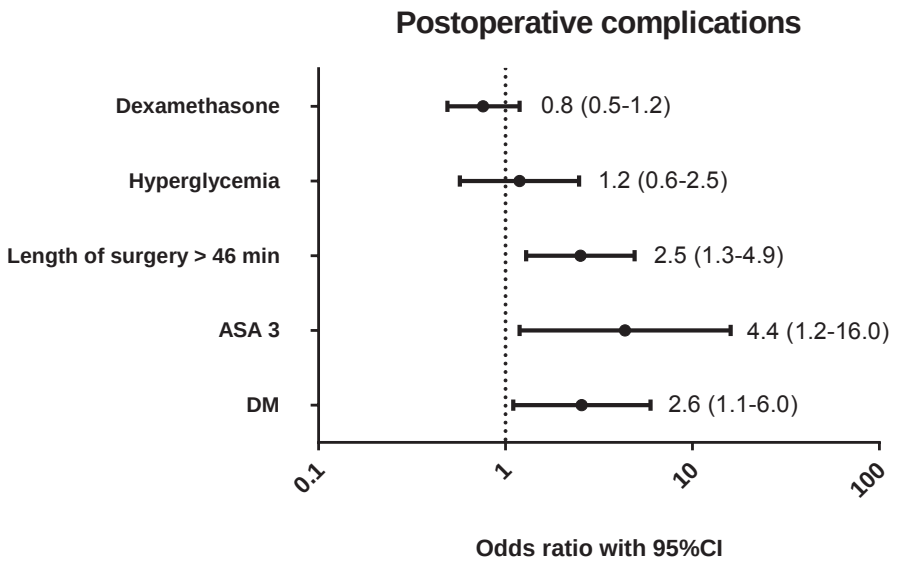

Figure 1. Risk factors for postoperative complications. Covariates included in the analysis were: gender, age, BMI, ASA-classification, diabetes, dexamethasone use, length of surgery and hyperglycaemia at any time during admission.

DM in itself was a significant risk factor for postoperative complications (OR 2.56, 95% CI 1.10-5.97, p=0.030, Figure 1) when adjusted for age, sex, BMI, ASA classification, dexamethasone use, hyperglycaemia and duration of surgery. Also, ASA 3 classification (OR 4.36, 95% CI 1.19-16.02, p=0.027) and duration of surgery (4th quartile >46 min, OR 2.52, 95% CI 1.29- 4.91, p=0.007) showed a significant association with postoperative complications. The use of dexamethasone was not associated with postoperative complications (OR 0.76, 95% CI 0.49 - 1.19, p=0.236).

Discussion

In this study we found a significant, but small increase of the median glucose from 5.4 to 5.6 mmol l^{-1} during ambulatory surgery. Plasma glucose of ≥7.8 mmol l^{-1} at any time during admission occurred in 8.8% of the patients. Risk factors for a perioperative increase

in glucose are a longer duration of surgery and the administration of dexamethasone during ambulatory surgery. Postoperative complications were increased in patients with hyperglycaemia; however after adjustment for confounders neither an increase in glucose during surgery, nor hyperglycaemia during admission was associated with postoperative complications. DM was associated with postoperative complications independent of hyperglycaemia.

The estimated prevalence of in-hospital hyperglycaemia in medical patients is 4-12% (11). In the present study, 8.8% of patients had hyperglycaemia during admission. After exclusion of patients with DM the incidence was 5.7%. This can be attributed to either undiagnosed DM, to a moderate/severe stress response or to the use of dexamethasone. When considering the ADA treatment guidelines for hyperglycaemia, 7 patients (0.8%) had a glucose >10 mmol l^{-1}. Thus, in minor ambulatory surgery it doesn't seem worthwhile to take additional measures with regard to blood glucose regulation. Furthermore screening for the sole purpose of diagnosing hyperglycaemia does not appear to be clinically relevant nor cost effective in patients without DM.

The risk factors for hyperglycaemia we found in our study are comparable to the 9 variables proposed by the ADA to identify patients who should be screened for DM (12). As the stress response due to ambulatory surgery seems to be minimal in the vast majority of the patients, the preoperative fasting state could be used as a screening opportunity for latent DM (13,14).

In patients without DM, a single dose of dexamethasone as prophylaxis for nausea and vomiting gives a significant but small and clinically irrelevant increase in median glucose in our study. The increase from baseline glucose is smaller as compared to studies in non-ambulatory surgery, which might be explained by the more invasive nature and longer duration of surgery (15-17).

Patients with DM had a significantly higher fasting glucose than patients without DM. However this was stable during surgery when no dexamethasone was administered and well below the target range of 10 mmol l^{-1} advocated by the ADA (18). Nonetheless, one has to keep in mind that in patients with DM glucose increased by 1.5 mmol l^{-1} after administration of dexamethasone. Although our sample size is limited, a similar increase in glucose in patients with DM who received a single dose of dexamethasone during surgery has been seen in a previous study (19). In our study, only DM was associated with postoperative complications independent of dexamethasone and hyperglycaemia, thus the clinical consequences of dexamethasone-induced hyperglycaemia in patients with DM could be questioned. We would suggest alternative postoperative nausea

and vomiting (PONV) prophylaxis in patients with DM. However, if multimodal PONV prophylaxis is indicated, we would not withhold dexamethasone in patients with DM, as long as glucose is monitored postoperatively and hyperglycaemia treated promptly. However, further research on this topic is needed.

A postoperative infection (8.1%) was the predominant postoperative complication in the study population. We used a broad definition of postoperative infection, ranging from seeking medical help for redness of the skin to initiation of antibiotics for postoperative fever. This may lead to an overestimation of surgical site infections and because of the self-reporting nature of the assessment, may be subjected to recall bias. Van Boxel et al. reported a similar rate of 7.6% of surgical site infections in patients with and without DM after laparoscopic cholecystectomy (20). In addition, 33% of these patients sought medical help within 30 days after discharge, although a postoperative complication was noted in just 15% of the patients (20), which is comparable to the 16% postoperative complications found in our study. The reported incidence of unexpected admissions after day-case surgery was between 2.7% and 6.7% (21-23) This is in accordance with our study population, of which 4.0% of the patients needed to be admitted or re-admitted within three months of surgery.

Interestingly, hyperglycaemia was not associated with postoperative complications, contrary to studies in major surgery (3-5). Because the incidence of hyperglycaemia was lower than expected, future studies are needed to confirm our findings. However, to illustrate the importance of the other different risk factors found in our study, we have calculated the theoretical risk of postoperative complications after ambulatory surgery in three different hypothetical male patients with a mean age and BMI, without administration of dexamethasone and with hyperglycaemia, using our multivariate regression model. An ASA 1 patient without DM and duration of surgery 46 minutes has a hypothetical 53.7% risk of any complication and the ASA 3 patient with DM and a duration of surgery >46 min has a 74.8% risk of developing a postoperative complication. This illustrates the possible clinical impact of duration of surgery, ASA classification and DM during ambulatory surgery.

This study has several limitations. First, we had a follow-up time of 90 days. Clinical trials investigating intensive insulin therapy range in follow-time from 30 days to 6 months (24). Although increasing the follow-up period might introduce recall bias, we also believe that it decreases the possibility of missing late complications. When available, we used chart reviews to minimize recall bias. Second, the loss to follow up was 26.3%. Patients were lost to follow up because of incorrect phone numbers or simply because patients did not answer their phone. However, this patient group was not significantly

different from patients who have been followed with regard to their perioperative glucose control and only including patients with complete follow up in the analysis did not change the results. Finally, the number of patients with DM was limited (N=7 DM1 and N=41 DM2, respectively). Excluding those patients who received insulin during surgery, did not change the results. Furthermore, this reflects the ambulatory surgery population in the Netherlands. Due to the low number of patients with DM, we were cautious with the interpretation of these results. Another potential source of bias was that seven patients (0.8%) drank glucose containing beverages 2 hours before glucose measurement, but excluding these patients from the analyses did not alter the results. This is the first study on stress hyperglycaemia during ambulatory surgery in a large patient population. Due to the prospective design of the study, measurement bias, e.g. measuring glucose on indication, was prevented. Furthermore, the characteristics of the study population are comparable to other ambulatory surgery studies in Europe with regard to age, ASA-classification and duration of surgery (25,26). The multicentre nature of the study makes it relevant for both academic and non-academic ambulatory settings.

Conclusions

Minor ambulatory surgery has no clinically relevant influence on overall glucose change in patients with and without diabetes. The glucose increase that does occur can be attributed to dexamethasone administration during surgery. Furthermore, glucose change and hyperglycaemia during ambulatory surgery are not associated with complications after discharge. However, patients with DM are at increased risk for postoperative complications after ambulatory surgery and the treating physician should be aware of this during follow-up visits.

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