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Perioperative hyperglycemic response to single-dose dexamethasone in patients undergoing surgery under spinal anesthesia

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Abstract

Background Dexamethasone is a potent corticosteroid when comes to effectively preventing postoperative nausea and vomiting (PONV). However, some studies have documented its association with hyperglycemia. In our study, we compared the effect of single-dose dexamethasone (8 mg) on blood glucose concentrations among diabetics and non-diabetic patients who received spinal anesthesia for elective lower abdominal and lower limb surgeries.

Results We recruited 80 patients and divided them into two groups of 40 patients each. After dexamethasone administration, diabetic patients had an early peak rise of blood glucose levels at 3 h, (157.85 ± 12.19) compared to 6 h, (125.30 ± 14.95) in non-diabetics. In diabetic patients, blood glucose levels remained consistently over the baseline and maximum rise was seen at 12 h (188.25 ± 41.33), which obviated the need or administration of injection insulin. Hyperglycemia can lead to a variety of physiological derangements.

Conclusions Although dexamethasone is a useful means of successful prevention and treatment of PONV, the clinician should use his clinical judgment before administering dexamethasone.

Trial registration CTRI, CTRI/2020/06/025765, Registered 02 June 2020, prospectively registered, http://ctri.nic.in/Clinicaltrials/login.php.

Keywords Dexamethasone, Diabetes mellitus, Hyperglycemia, Postoperative nausea, Vomiting

Background

Postoperative nausea and vomiting (PONV) remains a common undesirable experience with an overall incidence of 20-30% among the adults (Habib and Gan 2004; Watcha and White 1992). It results in delayed discharge and excessive medical expenditure. As a synthetic glucocorticoid, dexamethasone is one of the most commonly used drugs to prevent PONV (Watcha and White 1992; Peroutka and Snyder 1982). However, dexamethasone is known to cause perioperative hyperglycemia after a single dose. Perioperative hyperglycemia is related to increased gluconeogenesis, decreased insulin secretion from the pancreas, and insulin resistance caused by diminished peripheral glucose utilization (Pasternak et al. 2004; Rhee et al. 2004). The effects of perioperative hyperglycemia include dehydration, fluid shifts, electrolyte irregularities, infections, impaired wound healing, ketoacidosis, and hyperosmolar states.

In previous studies, dexamethasone administration led to a rise in postoperative blood sugar, which was comparable in diabetic and non-diabetic patients (Hans et al. 2006; Nazar et al. 2011) in another study, non-diabetic patients experienced higher intra-operative blood sugar levels than diabetics (Abdelmalak et al. 2013). In the

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perioperative period, the stress response can also cause hyperglycemia in non-diabetic patients. A choice of main anesthetic agent and technique can alter the stress response, reducing the release of stress hormones by modulating pathophysiologic pathways, as well as neurohormonal and immunologic responses (Desborough 2000). There is an increase in the plasma cortisol concentration during the perioperative period, ranging from 2 to 10 times. After surgery, this level usually returns to baseline levels within 24 h, but it may remain elevated for up to 72 h, depending on the severity of surgical trauma (Shaikh et al. 2012).

The effects of dexamethasone on perioperative glycaemic control in patients with diabetes has been a topic of debate for long time. As part of our study, we observed blood glucose variations for 48 h after dexamethasone administration to evaluate the perioperative hyperglycemic response to an antiemetic dose of dexamethasone, in diabetic and non-diabetic patients, undergoing elective lower abdomen and lower limb surgeries under spinal anesthesia.

Methods

A prospective, observational study was conducted on 80 patients of either sex, undergoing elective lower abdominal and lower limb surgeries under spinal anesthesia. Study participants were American Society of Anaesthesiologists (ASA) grade I and II patients, between the ages 30 and 60 years. After Institutional ethical clearance, the study was registered with Clinical Trials Registry-India with registration number CTRI/2020/06/025765.

Exclusion criteria for the study included patient's refusal, pregnancy, patients allergic to dexamethasone, recent treatment with steroids within last 48 h (Shin et al. 2020), Body mass index > 30 kg/m^2, intraoperative conversion from spinal to general anesthesia, uncontrolled fasting blood glucose (FBS > 130 mg/dl), bleeding diathesis, cardio-pulmonary comorbidity, and severe hepatorenal disease. After obtaining written informed consent, we allotted 40 non-diabetic patients to the non-diabetic group (group C) and 40 type 2 diabetes patients to the diabetic group (group D).

On the day of surgery, patients were fasted for 8 h. Inside the operation theatre, all patients were preloaded with 0.9% saline, followed by a continuous infusion at a maintenance rate according to the Holliday-Segar formula. Monitoring parameters included continuous heart rate (HR) electrocardiogram (ECG), hemoglobin oxygen saturation (SpO2), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP).All patients received injection Dexamethasone 8 mg intravenous (IV) bolus, immediately before administration of spinal anesthesia. We followed a standardized anesthetic technique for each case. Spinal anesthesia was administered in a sitting position, using aseptic precautions. Lumbar puncture was done at L3–L4 or L2–L3 intervertebral space with a 25 G BD^{TM} Quincke's spinal needle, through midline approach. After observing free flow of cerebrospinal fluid, 15–18 mg of 0.5% hyperbaric Bupivacaine was administered into the subarachnoid space. On confirming sensory blockade at T10 spinal level, surgery was commenced and continuous monitoring was done throughout the surgery, for any change in hemodynamic parameters.

In all patients, baseline blood glucose level was measured just before administration of injection dexamethasone, by the portable Accu-Chek® Active glucometer (Roche Diagnostics GmbH, Mannheim, Germany), finger-prick capillary blood samples, and labelled T0 in both the groups. Blood sugar levels were again measured hourly up to 3 h from T_0 and labelled T1, T2, and T3; then 6 hourly from T0 till next 12 h and 12 hourly up to 48 h. All hemodynamic parameters (SBP, DBP, MAP, HR, Spo2, and ECG) were recorded at baseline (T0), and subsequently at the time of each blood glucose measurement. C-reactive protein (CRP) was measured on the day of surgery (preoperative baseline values) and then at T24 and T48 to measure the effect of surgical stress.

Any adverse events during the study period were noted and treated accordingly. As the surgical procedures performed were superficial lower abdominal or lower limb surgeries, all the patients were started on oral feed 8 h after surgery, keeping in mind, the delayed gastric emptying in diabetic patients, due to autonomic neuropathy. When any patient's blood glucose level exceeded 180 mg/dl, he/she was administered injection insulin, according to the sliding scale, as advised by American Diabetic Association (ADA) guidelines for treatment of hyperglycemia.

Statistical analysis

The sample size was calculated by taking the mean of the blood glucose level change at 6 h after administration of dexamethasone (T_6) in the previous similar study (Purushothaman et al. 2018). The mean change in blood glucose levels at 6 h from baseline, was taken as 34.4 mg/dL in diabetics and 44.4 mg/dL in non-diabetics. We calculated the total sample size to be 80, at a 95% confidence interval (CI), using an alpha error of 5% and the power of 80%. The data were entered into the Microsoft Excel version 2016 and statistical analysis was performed by statistical software IBM© SPSS© (Statistical Package for the Social Sciences) version 25.0 (IBM© Corp., Armonk, NY, USA).

The quantitative values (numerical variables) have been presented in the form of mean and SD (mean ± SD) and the qualitative values (categorical variables) in the form of frequency and percentage (%). The Student *t* test has been used for comparing the mean values between the two groups, whereas the chi-square test is applied for comparing the frequency. *p* less than 0.05 is considered significant. The unpaired *t* test was used when two separate independent and identically distributed samples were obtained and a chi-square test was applied to compare the frequency. The calculated value was compared with the theoretical value of the chi-square distribution for the given degree of freedom to obtain the level of significance.

Results

The demographic parameters of patients included in the study are given in Table 1. In group D, the majority of patients were older, overweight, had multiple comorbidities, and had higher preoperative blood glucose concentrations. The duration of surgery was similar in both groups. Throughout the study period, blood glucose was significantly higher in diabetic patients than in non-diabetic patients. All patients in the study had significantly higher blood glucose levels subsequently. The diabetic patients had an earlier rise in blood glucose levels (at T3), as compared to non-diabetic patients (at T6). There was a significant rise in blood glucose in diabetic patients than the non-diabetic group (Fig. 1). The mean pre-operative values of CRP at T24 (0.59 ± 0.32) and T48 (0.73 ± 0.32) were significantly higher among group D patients compared to group C (Fig. 2).

Discussion

Dexamethasone, with the advantage of low cost, longer effectiveness, and better safety profile, is equally efficacious or superior for the prevention of PONV when compared with other preventive medications. The protective effect of dexamethasone for PONV was well supported in our study, with some incidences of postoperative hyperglycemia, in both diabetic and non-diabetic populations.

Table 1 Demographic parameters of patients

Demographic parameters	Group 'C'	Group 'D'	*P*
Age (years)	45.33 ± 8.75	49.43 ± 8.69	0.101
Gender (male/female) (%)	35 (87.5)/5 (12.5)	34 (85)/6 (15)	0.745
BMI (kg/m^2)	25.20 ± 3.03	26 45 ± 1.79	0.028
Comorbidities other than diabetes	5 (12.5%)	11 (27.5%)	< 0.001*
HbA1c(%)	5.62 ± 0.71	9.10 ± 1.85	< 0.001*
Preoperative blood glucose (T0)	97.03 ± 9.34	112.58 ± 9.78	< 0.001*
Duration of surgery (minutes)	72.25 ± 13.68	76.63 ± 17.99	0.224

$p < 0.05$ significant, *Group 'C'* non-diabetic group, *Group 'D'* diabetic group

Henzi et al. in their study found that dexamethasone in a dose of 8–10 mg IV, effectively prevents nausea and vomiting with effects most pronounced when administered before the induction of anesthesia (Henzi et al. 2000). In the multi-factorial trial by Apfel CC et al. dexamethasone, in doses, 4mg, was found similarly efficacious as ondansetron 4 mg and droperidol 1.25 mg, for prevention of PONV (Apfel et al. 2004).

In our study, we did not use a control group to which dexamethasone was not administered so to identify whether the hyperglycemia is due to dexamethasone or due to surgical stress, we performed C-reactive protein values in all our patients and found that CRP levels were also raised in postoperative period at 24 and 48 h (Fig. 2). Surgical stress due to prolonged surgeries is a known factor for hyperglycemia and could act as a confounder in the study. To counteract confounding due to surgical stress, we only included patients planned for superficial surgeries, that lasted for 1–2 h. Similar to our study, (Musba et al. 2015) found that surgery results in an increase in CRP plasma levels at the 24 h after surgery, irrespective of dexamethasone delivery ($p < 0.05$).

Due to its low cost, long duration of action, and apparent safety, 8 mg dexamethasone is increasingly being used as the agent of first choice (Henzi et al. 2000; Apfel et al. 2004) with ondansetron as a rescue antiemetic. When given before the surgical incision, dexamethasone efficiently prevents PONV with its anti-inflammatory action. Despite its benefits, regular use of dexamethasone as a premedication in anesthesia is constantly criticized due to concerns about steroid-induced hyperglycemia and related effects on a postsurgical patient.

In our study, dexamethasone caused more hyperglycemia in diabetic patients compared to non-diabetics. These results were akin to the results of the study by (Allen et al. 2020) and (Herbst et al. 2020), which determined that preoperative dexamethasone was associated with hyperglycemia and increased insulin requirements in diabetic patients, in the immediate postoperative period. However, (Godshaw et al. 2019) found that perioperative higher blood glucose levels were related not to the use of dexamethasone but instead to an elevated glycosylated hemoglobin concentration (HbA1c) and poorly controlled blood glucose in the preoperative period. (Pasternak et al. 2004) also attributed the increase in blood glucose levels to surgical stress response and suggested that intraoperative blood glucose concentrations should

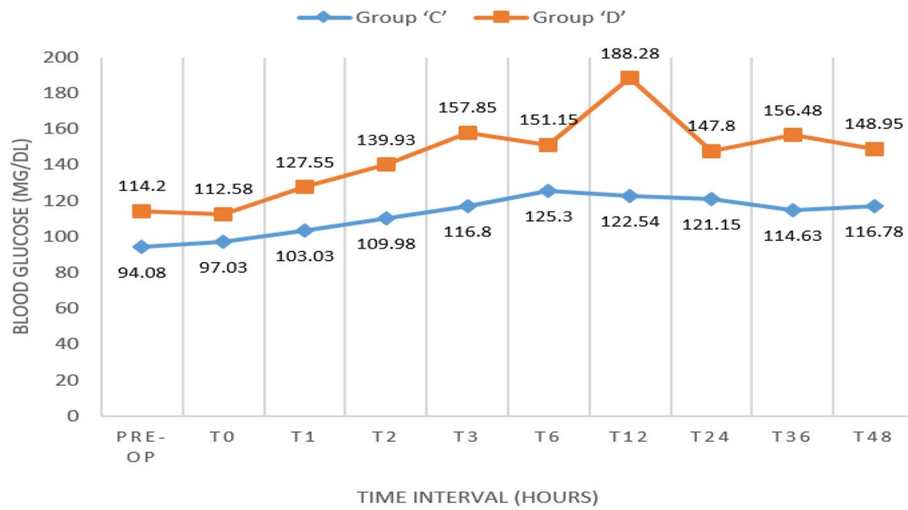

Fig. 1 The time course of mean blood glucose concentrations in the two groups

be carefully monitored and hyperglycemia to be treated, if dexamethasone is used during craniotomy.

Contrary to our findings, a previous study by (Purushothaman et al. 2018) found that non-diabetics are more susceptible to hyperglycemia after dexamethasone administration. The rise in blood glucose started 3 h after the administration of dexamethasone, with a sustained increase afterward, which is similar to the changes found in our study. They could not find any difference in the magnitude of the increase in blood glucose between the diabetic and the non-diabetic patients. Lukins MB et al. (Lukins and Manninen 2005) also demonstrated similar findings with non-diabetics being more susceptible to developing hyperglycemia as compared to diabetics, after administration of a single dose of IV dexamethasone (8 mg).

In our study, blood sugar in non-diabetic subjects, peaked at 6 h (T6), while the diabetic patients showed peak levels at 3 h (T3) when both the groups were still fasted. After allowing oral feeds at 8 h after surgery, diabetic patients exhibited a greater rise in blood sugar levels as well as a tendency to develop hyperglycemia (blood sugar > 180 mg/dl). A total of 32 patients in the diabetic group developed hyperglyecemia, out of which 6 patients showed hyperglycemia on two or more occasions. In all occasions, regular human insulin (sliding scale) was administered, as advised by American Diabetic Association (ADA) guidelines. However, there was no significant rise in blood sugar values in non-diabetic patients.

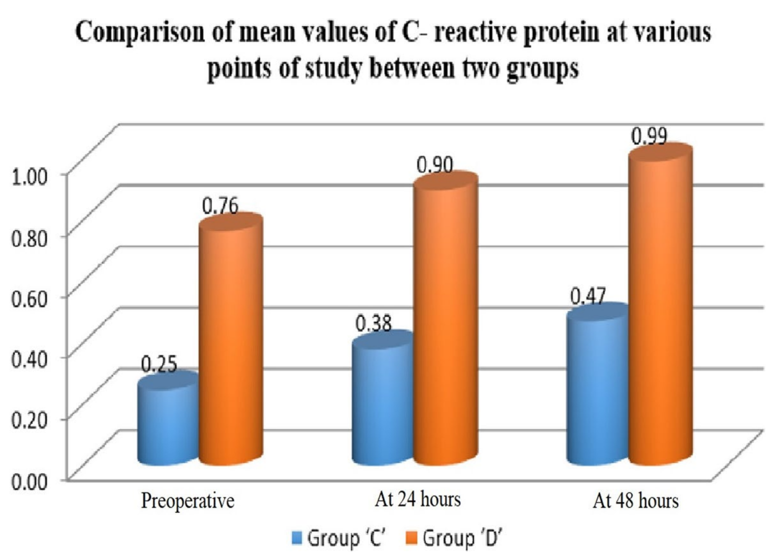

Fig. 2 Comparison of mean values of C-reactive protein at various points of study

The actual cause of the rise in blood sugar can be attributed to the composition, frequency, and timings of the meal, and to the level of physical activity in each patient. Moreover, every patient responds differently to the perioperative stress of surgery and anesthesia. The other culprit responsible for variation in the rise in blood sugar in the postoperative period could be oral hypoglycaemic agents (OHA), for which we did not standardize the class, frequency, dose, or the time interval between intake of OHA and food.

When compared to placebo, there is probably little or no difference in the risk of postoperative infection with dexamethasone (Kelbel et al. 2001). However, glucose level disruption may lead to infections, and the risk is higher in diabetic patients. Often these infections result in revision surgeries which have a substantial economic burden, decrease patient quality of life, and may expose patients to the risks of subsequent revisions. The use of dexamethasone in patients with diabetes can be considered if the benefits outweigh the risks. Further studies focusing on pain control, PONV, and glucose level disruption in diabetic patients will better clarify the concerns surrounding dexamethasone administration.

Conclusions

Despite the benefits of dexamethasone for prophylaxis of PONV, concerns of steroid-induced glucose level disruption and hyperglycemia cannot be excluded, especially in diabetic patients. The clinician should use dexamethasone for prophylaxis of PONV after careful assessment of the risk-benefit ratio and using his clinical judgment.

Limitation of study

1. Our study was limited to ASA I and II patients and could not be implemented to the general population.
2. Duration of surgery was limited to 60–120 min.
3. Our study population size was small ($N = 80$) to find out a significant amount of variation in a large population.
4. Every patient in our study was allowed oral feed after 8 h, which resulted in higher blood sugar levels.
5. The frequency of OHA and insulin, in our study was not standardized.
6. The postoperative follow-up period of our study was limited to 48 h only.

Abbreviations

PONV	Postoperative nausea and vomiting
BMI	Body mass index
GIT	Gastrointestinal tract
CO2	Carbon dioxide
ASA	American society of Anaesthesiologists
ECG	Electrocardiogram
kg	Kilogram
Mg	Milligram
Mm	Millimeter
IV	Intravenous
SD	Standard deviation
VAS	Visual analog score
CRP	C-reactive protein
HbA1c	Glycosylated hemoglobin concentration
DM	Diabetes mellitus
ND	Non-diabetic
CI	Confidence interval
FBS	Fasting blood sugar
ADA	American Diabetic Association
PACU	Post-anesthesia care unit

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Authors' contributions
KNJ compiled data and obtained ethical approval. AKC contributed to the statistical analysis and interpretation of data. UP contributed to the discussion. All authors have read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval for the said study was obtained from Institutional Ethics Committee of Government Medical College, Haldwani under letter no. 436/GMC/IEC/2018/Reg.No.390/ IEC/R-08-10-2018. Informed written consent to participate in the study was provided by all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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