ABSTRACT

Background: Dexamethasone is a potent corticosteroid when administered alone or in combination alone has proven efficacious in preventing nausea and vomiting (PONV) perioperatively. However, the administration of even a single dose has been associated with hyperglycemia. This is the first study that evaluates the effect of two low-doses of dexamethasone (4 and 8 mg) on blood glucose concentrations among diabetics and nondiabetics in patients who have received spinal anesthesia.

Materials and Methods: After obtaining ethical clearance and patient consent, 180 American Society of Anesthesiologists 1–3 patients undergoing the elective infraumbilical surgeries under spinal anesthesia aged between 18 and 70 years were included in this study. Ninety diabetic patients were allotted to the diabetic group (DM), and ninety nondiabetic patients were allotted to the nondiabetic group (ND). Group DM was divided into three subgroups DM0, DM4, and DM8. Group ND was divided into three subgroups ND0, ND4, and ND8. The patients in groups DM0 and ND0 served as controls. The patients in groups DM4 and ND4 received 4 mg dexamethasone. The patients in groups DM8 and ND8 received 8 mg dexamethasone. The blood glucose concentrations were monitored at 0 (baseline), 1, 2, 3, 4, 5, 6, and 8 h after giving the drug.

Results: The baseline blood glucose values were higher in diabetics compared to nondiabetics (128.57 ± 22.26 vs 94.99 ± 12.82 mg/dL). There was a statistically significant increase in blood glucose concentrations in both diabetics and nondiabetics who received dexamethasone. The rise of blood glucose from baseline was similar in both diabetics and nondiabetics.

Conclusion: The maximum rise in blood glucose was in the range of 40–45 mg/dl in the patients who received dexamethasone. The clinician should use his clinical judgment before administering dexamethasone for PONV prophylaxis/treatment.

Key words: Dexamethasone; diabetes mellitus; hyperglycemia; postoperative nausea and vomiting

Introduction

Neuraxial opioids are commonly used for providing postoperative analgesia and have many advantages over parenteral narcotics. Buprenorphine is a long-acting, highly lipophilic opioid which has proved to be an excellent analgesic adjuvant for neuraxial blocks. Buprenorphine offers the advantage of providing good analgesia while allowing early ambulation of the patient by sparing sympathetic and motor...
The use of buprenorphine has been associated with postoperative nausea and vomiting (PONV). For PONV prophylaxis, dexamethasone 4 mg intravenous (IV) has been found to be as efficacious as ondansetron 4 mg IV and droperidol 1.25 mg IV. There are some recent studies that have found that a dose of dexamethasone 8 mg IV rather than a dose of 4 mg is more beneficial for PONV prophylaxis. Preoperative dexamethasone 8 mg has been found to have additional benefits like it improves the postdischarge quality of recovery in addition to reducing nausea, pain, and fatigue.

A single-dose of dexamethasone is however known to increase the blood glucose levels in the perioperative period. Hyperglycemia in the perioperative period can cause dehydration, fluid shifts, electrolyte abnormalities, predisposition to infection, impaired wound healing, ketoacidosis, and hyperosmolar states. Hence, although dexamethasone is proven effective for the prophylaxis and treatment of PONV, clinicians have some reluctance to use it due to the fear of hyperglycemia. The literature with respect to the use of dexamethasone in diabetic patients is limited.

This is the first study that looks into the blood glucose variations in the first 8 h after administration of dexamethasone in diabetics and nondiabetics undergoing surgeries under spinal anesthesia.

Materials and Methods

A prospective, randomized, placebo-controlled study was conducted in 180 patients of either sex undergoing elective lower extremity and infraumbilical surgeries. The patients of American Society of Anesthesiologists Grade 1–3 aged between 18 and 70 years were included in the study. Patients who had recent parenteral or oral steroid therapy or those who had received a dose of steroid within last 48 h, allergy to dexamethasone, and intraoperative conversion to general anesthesia were excluded from the study. The patients satisfying the inclusion criteria were selected by random number table during the study from the operation theater register on a daily basis. Institutional ethical clearance was obtained, and the study was registered with Clinical Trials Registry-India with registration number CTRI/2017/03/008150. After obtaining a written informed consent, ninety type 2 diabetes patients were allotted to the diabetic group (DM) and ninety nondiabetic patients to the nondiabetic group (ND). Further, patients in each group were allotted into one of the three subgroups of thirty each by a sealed envelope, the subgroups being DM 0, DM 4, and DM 8 in the DM group and ND 0, ND 4, and ND 8, in ND group. The patients in groups DM 0 and ND 0 were the control groups that received 5 ml normal saline. The patients in groups DM 4 and ND 4 received 4 mg dexamethasone. The patients in groups DM 8 and ND 8 received 8 mg dexamethasone.

All the patients received oral pantoprazole 40 mg as premedication on the night before and on the day of the surgery. Perioperative monitoring included electrocardiogram, noninvasive blood pressure monitor, and pulse oximetry. An 18-gauge intravenous (IV) cannula was inserted, and normal saline infusion was instituted. Midazolam 1 mg was administered following placement of IV line. The test drugs were diluted with normal saline to achieve a volume of 5 ml and were administered over 30 s intravenously immediately before performing spinal anesthesia. An independent investigator prepared and administered the study drugs. Patients, anesthesiologists involved in intraoperative care, and investigators collecting postoperative data were blinded to patient group allocation.

A standardized anesthetic technique was followed. Spinal anesthesia was administered in the sitting position. Using an aseptic technique, a 25-gauge Quincke needle was inserted through a midline approach into the L2–L3 or L3-L4 interspace. Anesthesia was established with a single bolus of 0.5% hyperbaric bupivacaine 15 mg and buprenorphine 60 mcg. The level of sensory blockade was assessed regularly by the level of touch sensation before surgical incision (T6–T8 was considered adequate). Additional midazolam 1–2 mg IV was administered for intraoperative sedation on attending anesthesiologist’s discretion. Supplemental oxygen 5 L/min through a face mask was administered during the surgery. Estimated fluid requirement and maintenance fluid were replaced with Ringer’s lactate or 0.9% normal saline. A standard postoperative analgesic regimen of paracetamol 1 g IV infusion 6th hourly and tramadol 50 mg IM as required was prescribed for postoperative pain relief.

Finger-prick capillary blood glucose was measured immediately before dexamethasone administration (T0) and at 60 (T1), 120 (T2), 180 (T3), 240 (T4), 300 (T5), 360 (T6), and 480 (T8) min thereafter using a glucometer. Glucose level...
measurements were made by a finger-prick capillary blood sample using an Accu-Chek® Active (Roche Diagnostics GmbH, Mannheim, Germany) glucometer that was calibrated daily. Postoperatively, patients were administered dextrose-free IV fluids at 2 ml/kg/h till the study ended 8 h after dexamethasone administration. No dextrose-containing solution was administered during the study.

Statistical methods

Sample size calculation

Based on the previous study, it was found that the mean ± standard deviation (SD) change from preoperative to maximal intraoperative glucose concentration was 63 ± 66 mg/dL in diabetics and 86 ± 41 mg/dL in nondiabetics. In the present study, expecting mean glucose change as 23 mg/dL between the two groups with an effect size of 0.4 and an alpha error of 5% with power of 80% the sample size was estimated to be ninety in DM and ninety in ND.

Descriptive and inferential statistical analysis has been carried out in the study. Results on continuous measurements are presented as mean ± SD, and results on the categorical measurements are presented in number (%). Significance was assessed at 5% level of significance. Analysis of variance has been used to find the significance of study parameters between three or more groups of patients, and post hoc analysis between the groups was done by Fisher’s least square difference test. Student’s t-test (two-tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Intergroup analysis) on metric parameters. Chi-square/Fisher’s exact test has been used to find the significance of study parameters on categorical scale between two or more groups. P < 0.05 has been considered as statistically significant. Statistical software Statistical software IBM® SPSS® (Statistical Package for the Social Sciences) version 18 (IBM © Corp., Armonk, NY, USA) was used for the analysis of the data; Microsoft Word and Excel have been used to generate graphs and tables.

Results

We recruited a total of 180 patients in the study. The patient demographic data are presented in Table 1. In the DM group there were older patients, with a greater body weight, more comorbid diseases, and with higher preoperative blood glucose concentrations which were statistically significant. This was expected as majority of diabetic patients are older, overweight, and have multiple comorbidities. The duration of surgery was similar in both the groups. Throughout the study period, blood glucose was significantly higher in diabetic than in nondiabetic patients. All patients in the study who received dexamethasone had significantly higher blood glucose levels subsequently [Tables 2 and 3]. The nondiabetic patients who received 8 mg of dexamethasone had significantly earlier rise of blood glucose levels (at T3) compared to placebo, and blood glucose was higher than

Table 1: Demographic data

|                  | ND     | Diabetic | P     |
|------------------|--------|----------|-------|
| Age (years)      | 45.84±14.26 | 61.13±5.97 | <0.001* |
| Female/male (%)  | 27 (30)/63 (70) | 29 (32.2)/61 (67.8) | 0.747   |
| Weight (kg)      | 63.55±9.05 | 67.28±8.22 | 0.004*  |
| Comorbidities other than DM (%) | 17 (18.9) | 42 (46.7) | <0.001* |
| Preoperative blood glucose (mg/dl) (T0) | 94.99±12.82 | 128.57±22.26 | <0.001* |
| Surgical specialty |        |          |       |
| General surgery  | 62     | 71       |       |
| Gynecology       | 12     | 12       |       |
| Orthopedics/plastic and others | 26 | 17 |       |
| Duration of surgery (min) | 72.83±26.86 | 74.27±28.17 | 0.725   |

*P<0.05 significant. DM: Diabetes group; ND: Nondiabetic group

Table 2: Blood glucose concentrations during the study in diabetics (mg/dl)

| Time  | Group DM0 | Group DM4 | Group DM8 | P     |
|-------|-----------|-----------|-----------|-------|
| T0    | 134.37±22.76 | 125.57±21.02 | 125.77±22.55 | 0.219 |
| T1    | 139.30±24.51 | 137.67±19.95 | 135.63±26.13 | 0.835 |
| T2    | 141.17±25.42 | 149.30±20.64 | 143.33±27.95 | 0.426 |
| T3    | 138.47±25.95 | 161.33±20.49 | 154.23±34.15 | 0.006*  |
| T4    | 147.27±23.64 | 169.27±21.75 | 166.80±25.91 | <0.001* |
| T5    | 144.37±22.89 | 165.03±21.41 | 167.53±18.63 | <0.001* |
| T6    | 146.93±20.77 | 158.03±25.38 | 160.23±15.98 | 0.037*  |
| T8    | 144.47±20.62 | 151.17±20.80 | 149.10±17.02 | 0.401   |

P<0.05 significant between the three groups by analysis of variance. Post hoc analysis between the groups was done; †P<0.05 significant between DM0 and DM4; ‡P<0.05 significant between DM0 and DM8. T0 (baseline), T1 (60), T2 (120), T3 (180), T4 (240), T5 (300), T6 (360), and T8 (480) min after test drug administration. DM: Diabetes group

Table 3: Blood glucose concentrations during the study in nondiabetics (mg/dl)

| Time  | Group ND0 | Group ND4 | Group ND8 | P     |
|-------|-----------|-----------|-----------|-------|
| T0    | 96.23±11.24 | 93.27±11.60 | 95.47±15.45 | 0.654 |
| T1    | 99.70±12.28 | 98.40±14.84 | 98.47±13.77 | 0.918 |
| T2    | 102.07±13.43 | 104.93±18.92 | 104.77±15.25 | 0.739 |
| T3    | 104.93±15.11 | 114.87±19.34 | 116.93±21.17 | 0.034*  |
| T4    | 100.93±23.71 | 126.63±23.26 | 129.40±25.26 | <0.001* |
| T5    | 103.07±24.53 | 133.10±26.07 | 137.83±23.82 | <0.001* |
| T6    | 103.67±15.28 | 124.30±24.51 | 139.87±27.86 | <0.001*  |
| T8    | 100.27±15.03 | 114.60±21.34 | 133.10±28.08 | <0.001*  |

*P<0.05 significant between the three groups by analysis of variance. Post hoc analysis between the groups was done; †P<0.05 significant between ND0 and ND4; ‡P<0.05 significant between ND0 and ND8. T0 (baseline), T1 (60), T2 (120), T3 (180), T4 (240), T5 (300), T6 (360), and T8 (480) min after test drug administration. DM: Diabetes group
those who received 4 mg after 6 h [Table 2]. Although there was a significant rise in blood glucose in the diabetic patients who received both doses of dexamethasone compared to placebo, the DM8 group did not have higher blood glucose values than DM4 group during the study. The time course of blood glucose concentrations in the two groups is shown in Figure 1. In the patients who received dexamethasone 4 mg, blood glucose peaked at T4 and T5 in the diabetics and NDs, respectively. In the patients who received dexamethasone 8 mg, blood glucose peaked at T5 and T6 in the diabetic and NDs, respectively.

We plotted the rise of blood glucose from the baseline and found that magnitude of rise was similar in both diabetics and nondiabetics who received dexamethasone. Both the diabetic and nondiabetic control groups did not have a clinically significant hyperglycemic response; it was in the range of 10–15 mg/dl from the baseline [Figure 2]. The rise of blood glucose from baseline was compared between the diabetic and nondiabetic subgroups at T4 and T8 [Table 4]. The rise of blood glucose from baseline was statistically significant at T4 in diabetics who received 4 mg of dexamethasone. The patients who received 8 mg of dexamethasone the rise of blood glucose was similar in both diabetics and nondiabetics at T4. However, at T8, the nondiabetic patients who received 8 mg dexamethasone had statistically significant rise in blood glucose levels in comparison with diabetics who received a similar dose. There were only three patients in our study whose blood glucose were more than 200 mg/dl during the study, one each from the ND4, ND8, and DM8 groups, the highest blood glucose being 234 mg/dl at 5 h postdexamethasone 4 mg administration in a nondiabetic patient.

**Discussion**

In our study, dexamethasone administration for PONV prophylaxis resulted in significant elevation of blood glucose in both diabetic and nondiabetic patients. The rise of blood glucose started 3 h after the administration of dexamethasone, and patients had a sustained rise till 8 h after. The magnitude of increase was not very different between the diabetic and the nondiabetic patients.

Hans et al. in their study analyzed blood glucose levels in the first 6 h postoperatively in nondiabetics, and patients with type 2 diabetes receiving IV dexamethasone 10 mg for PONV prophylaxis, they found that blood glucose concentration profile although parallel, was significantly higher in type 2 diabetic than in nondiabetic patients and peaked 120 min after injection.[14] However, their study did not have a control group that did not receive dexamethasone, to differentiate if the hyperglycemic response was secondary to the administration of dexamethasone or to the surgical stress response. In

- **Table 4: The mean rise of blood glucose from baseline at T4 (4 h postdexamethasone administration) and at T8 (8 h postdexamethasone administration)**

| Time | Groups | Rise from baseline (mg/dl), mean±SD (%) | P  |
|------|--------|----------------------------------------|----|
| T4   | ND0    | 4.70±23.58 (4.88)                      | 0.129 |
|      | DM0    | 12.90±17.18 (9.60)                     |     |
|      | ND4    | 33.37±20.37 (35.77)                    | 0.038* |
|      | DM4    | 43.70±17.34 (34.80)                    |     |
|      | ND8    | 33.93±22.00 (35.54)                    | 0.146 |
|      | DM8    | 41.03±14.64 (32.62)                    |     |
| T8   | ND0    | 4.03±9.95 (4.20)                       | 0.061 |
|      | DM0    | 10.10±14.30 (7.52)                     |     |
|      | ND4    | 21.33±21.20 (22.87)                    | 0.412 |
|      | DM4    | 25.60±18.78 (20.39)                    |     |
|      | ND8    | 35.63±23.21 (37.32)                    | 0.041* |
|      | DM8    | 23.33±22.39 (18.55)                    |     |

*P<0.05 significant. T4 (240) and T8 (480) min after test drug administration.

SD: Standard deviation; DM: Diabetes group; ND: Nondiabetic group

**Figure 1: Blood glucose concentrations during the study period (mg/dl).**

**Figure 2: The mean rise of blood glucose from baseline (mg/dl).**

T0 (baseline), T1 (60), T2 (120), T3 (180), T4 (240), T5 (300), T6 (360), and T8 (480) minutes after test drug administration.
our study, we found that the hyperglycemic response in both diabetic and nondiabetic patients who did not receive dexamethasone was in the range of 10–15 mg/dl. However, patients who received dexamethasone had significant rise in blood glucose in the range of 40–43 mg/dl which peaked between 4 and 6 h postdexamethasone administration. These findings are similar to that of Nazar et al. where thirty obese patients who received 8 mg dexamethasone had higher maximum blood glucose concentrations (187 mg/dl) compared with controls (158 mg/dl).[15] However, a drawback of that study is that they have infused glucose-containing IV fluids during the study.

There have only been a few studies that investigated the hyperglycemic effects of dexamethasone in the postoperative period in patients with type 2 diabetes, in all the studies general anesthesia has been used.[14–19] Ours is the only study where spinal anesthesia has been used to study the hyperglycemic response to dexamethasone. Spinal anesthesia has been proved to be more effective than general anesthesia in suppressing stress and glycemic response in elective surgical patients.[20] The addition of buprenorphine has been found to prolong the duration of spinal analgesia to 7.44 ± 1.69 h.[21] The control groups in our study had a blunted hyperglycemic response during the study, but the groups that received dexamethasone had a significant hyperglycemic response.

Similar to our findings, Nazar et al. in another study demonstrated that diabetic patients did not show higher susceptibility than nondiabetics to develop postoperative hyperglycemia after the use of prophylactic dexamethasone 8 mg for PONV[16] Contrary to our study where both groups had a hyperglycemic response, the findings of another study found that there was no dexamethasone-induced hyperglycemic effect for diabetic patients and nondiabetic patients showed a greater increase in blood glucose level.[17] Low et al. in a retrospective database study found that dexamethasone 8–10 mg was associated with a significantly greater perioperative increase in blood glucose compared with a 4 mg dose.[18] Tien et al. showed that PONV prophylaxis with IV dexamethasone (8 mg) significantly increases postoperative blood glucose values compared with ondansetron (4 mg).[19] This effect was comparable between nondiabetic and diabetic patients, regardless of baseline blood glucose levels. Our study also had similar findings where 4 and 8 mg of dexamethasone increased the blood glucose levels in both diabetics and nondiabetics. Nondiabetics who received 8 mg of dexamethasone had significantly higher rise in blood glucose levels compared to diabetics who received the same dose at 8 h.

Our study has a few limitations the diabetic patients were older and had more comorbidities, and we have not selected the matched controls. Second, the blood glucose measurements were performed using a portable point-of-care glucometer. Third, we have monitored blood glucose levels for first 8 h, and after this, any increase in blood glucose levels might have been missed. Furthermore, patients undergoing different types of surgery were included, and postoperative stress response may be varied following different types of surgery. In our study, 8 mg of dexamethasone caused a greater magnitude of hyperglycemic response in nondiabetics when compared with diabetics. The reason for this cannot be explained.

Conclusion

That PONV prophylaxis with IV dexamethasone 4 or 8 mg significantly increases blood glucose values compared to placebo. Dexamethasone 8 mg causes a greater hyperglycemic response in nondiabetics compared to diabetic patients at 8 h postadministration. Diabetics have an exaggerated hyperglycemic response at 4 h postdexamethasone 4 mg administration. However, the maximum rise in blood glucose was in the range of 40–43 mg/dl in patients who received dexamethasone 4/8 mg, and the clinician should use his clinical judgment before administering dexamethasone for PONV prophylaxis/treatment.

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Conflicts of interest
There are no conflicts of interest.

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