**Effect of a single intraoperative dose of dexamethasone on glycaemic profile in postoperative patients - A double-blind randomised controlled study**

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**ABSTRACT**

**Background and Aims:** The effect of a single intraoperative dose of steroids on perioperative blood sugar levels is uncertain. We hypothesised that a single dose of dexamethasone would not unfavourably alter the glucose levels of non-diabetic patients. This study aimed to evaluate the post-operative glycaemic profile after a single dose of intraoperative dexamethasone in non-diabetic patients. The presence of post-operative nausea and vomiting (PONV), pain, surgical site infection (SSI) and length of hospital stay were also evaluated. **Methods:** This randomised, double-blind, controlled study was done by recruiting 150 non-diabetic adult patients of the American Society of Anesthesiologists physical status I/II undergoing elective surgery. Patients in the study group were administered a single dose of dexamethasone (0.15 mg/kg). Blood glucose levels were assessed at various time points for up to 72 hours post-operatively using point-of-care testing. Secondary outcomes such as PONV, pain, fever and SSI were also documented. Data were compared and analysed using Student's t-test, Chi-square test, Mann-Whitney test and analysis of variance test. **Results:** There was an earlier, higher and prolonged elevation in blood glucose levels in patients receiving dexamethasone. The mean (standard deviation) of fasting/postprandial blood sugars on the first, second and third postoperative days respectively was significantly higher in the study group 98.04 (21.89)/139.16 (20.59), 96.64 (19.20)/138.17 (18.05), 96.60 (17.40)/138.32 (15.10) mg/dl as compared to control group 86.9 6 (10.28)/128.95 (10.53), 88.81 (8.87)/131.97 (9.48) mg/dl. About 10.7% of the patients who received dexamethasone had blood glucose levels greater than 180 mg/dl. There were no significant differences in the secondary outcomes. **Conclusion:** Even a single dose of dexamethasone in non-diabetic adults causes significant and prolonged postoperative hyperglycaemia.

**Key words:** Dexamethasone, hyperglycaemia, intraoperative period, postoperative period

**INTRODUCTION**

A single dose of dexamethasone is often administered in the intraoperative period for its anti-inflammatory, antiemetic, analgesic and immunomodulatory effects. Perioperative steroids are known to drive blood glucose levels above the generally accepted inpatient goals, due to increased insulin resistance and reduced function of the pancreatic beta-cells.

Hyperglycaemia is associated with increased morbidity and mortality, especially in critically ill patients. A retrospective study by Herbst et al. found that the administration of a single dose of dexamethasone, raised blood sugar levels transiently, without any adverse patient outcomes. Existing...
data on the changes in glycaemic profile is restricted to the intraoperative and the first 24 hours of the post-operative period. Considering the longer biological half-life of dexamethasone (36 to 54 hours), there is a paucity of prospective studies on the prolonged impact of a single dose of dexamethasone on the perioperative blood glucose levels for the entire period.

We hypothesised that a single intraoperative dose of dexamethasone does not affect the perioperative glycaemic profile of non-diabetic adult patients. Our primary objective was to compare the changes in the glycaemic profile (up to 72 hours post-operatively) that occur in patients receiving a single dose of dexamethasone. Secondary outcomes such as postoperative nausea and vomiting (PONV), pain, fever, surgical site infection (SSI) and length of stay (LOS) in the hospital were also assessed.

METHODS

This double-blind, randomised, controlled study was done in a tertiary care centre and teaching institute from February 2019 to June 2020 after institutional ethics committee approval (ref: 50/18/IEC/JMMC&RI) following the principles of the declaration of Helsinki. The trial was registered with the Clinical Trials Registry of India (CTRI/2019/02/017570). The study was powered using postoperative hyperglycaemia as the primary outcome. Based on the proportion of hyperglycaemic patients observed in an earlier publication by Pasternak et al. with a 95% confidence level and 90% power, the minimum sample size required was 75 in each group. To compensate for fallouts, we enrolled a total of 155 patients. One fifty patients aged between 18 - 70 years, of the American Society of Anesthesiologists physical status (ASA PS) I or II, posted for elective middle ear surgery were recruited and studied for 72 hours.

After taking informed written consent, the patients were randomly allotted to one of the two groups, by computer-generated block randomisation (“Random UX” computer application, UXapps, Cyprus). Patients in the study group (group A) received dexamethasone, whereas participants in the control group (group B) received a placebo. Double blinding was ensured by using preloaded 5 ml syringes of dexamethasone of 2 mg/ml dilution (labelled A) and saline (labelled B), prepared by a nurse unaware of allocation.

On arrival in the operating room, routine monitoring devices (non-invasive blood pressure, capnogram, electrocardiogram and pulse oximetry) were attached. The pre-anaesthetic regimen, anaesthesia procedure and surgical techniques were uniform for all subjects. Patients were premedicated with intravenous (IV) glycopyrrolate 0.2 mg, ondansetron 4 mg and midazolam 1 mg. All patients received standardised general anaesthesia consisting of IV induction using propofol 2 mg/kg, atracurium 0.5 mg/kg and fentanyl 2 µg/kg. Endotracheal intubation was performed in all subjects. Following intubation, group A received a single dose of IV dexamethasone (0.15 mg/kg to a maximum of 8 mg), whereas group B received saline as placebo/control. Anaesthesia was maintained with atracurium and a mixture of oxygen, air and sevoflurane. All candidates received IV paracetamol 1 gm for postoperative analgesia. At the end of the surgery, all patients were
extubated after reversing neuromuscular blockade with IV neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. All patients were given Ringer’s lactate perioperatively. Titrated doses of fentanyl were given in the postoperative period.

The parameters recorded were blood glucose, postoperative pain, incidence of postoperative nausea/vomiting and infection at the surgical site. All blood glucose levels were measured using a calibrated glucometer (On Call Plus glucometer, Acon Labs, USA). Blood sugar was again recorded two hours after administration of the drug/placebo. The FBS and PPBS values of the first, second and third postoperative days (PODs) were also documented.

Postoperative pain was assessed using a visual analogue scale ranging from 0 “no pain” to 100 “the worst imaginable pain.” The time of demand for the first rescue analgesic (IV fentanyl) following surgery and a cumulative analgesic requirement on POD1 were also noted. The severity of PONV was assessed using a 4-point verbal descriptive scale which consists of score 0 = no PONV; no complaint of nausea or vomiting; score 1 = mild PONV: patient complains of nausea but refuses antiemetic treatment; score 2 = moderate PONV: patient complains of nausea and needs antiemetic treatment; score 3 = severe PONV: patient complains of nausea with episode of vomiting requiring antiemetic treatment.[6] SSI was assessed throughout the LOS and diagnosed if any of the criteria in Centre for Disease Control guidelines were met.[7]

Blood sugar values two hours after dexamethasone/placebo administration as well as FBS and PPBS on POD 1, 2 and 3 were taken as primary endpoints. Analgesic consumption and PONV scores on POD1 as well as fever and wound site infection were the secondary endpoints.

All analysis was conducted by a statistician using computer software (International Business Machines (IBM) Statistical Package for Social Sciences statistics for Windows, version 25.0, Chicago, USA). While performing descriptive analysis, numerical variables were expressed as mean (standard deviation), whereas categorical values were expressed as frequency and percentages. The median was also calculated as the data was skewed. Quantitative data were compared using Student’s t-test and chi-square test. Mann-Whitney test and analysis of variance test were used to find the association between continuous data. The correlation was calculated using Pearson’s correlation coefficient (for normally distributed data) and Spearman’s rho correlation coefficient (if data was not normally distributed). We tested if there was an overall significant difference between the means at different time points. When the data violated the assumption of sphericity, the results were validated using Greenhouse Geisser correction. Bonferroni test was used to reduce type 1 errors. A P value less than 0.05 was considered statistically significant.

RESULTS

The groups were comparable as regards the patient demographics [Table 1]. A total of nine patients had a family history of diabetes mellitus; five were in the study group and four in the control group (P = 0.731). The HbA1c levels were comparable in both groups. The mean baseline FBS level was 84.33 (11.12) mg/dl in the study group versus 84.44 (9.02) mg/dl in the control group (P = 0.949).

The mean dose of dexamethasone used in the study group was 7.9 (0.16) mg.

The blood sugar readings taken two hours after administration of dexamethasone/placebo were 93.76 (10.23) and 93.71 (9.33) mg/dl in the study and control groups respectively (P = 0.97)

During the postoperative period, FBS and PPBS values were significantly higher in the study group for up to 72 hours [Figures 2 and 3]. Mean FBS in the study group was 98.04 (21.89) mg/dl on POD1, 96.64 (19.2) mg/dl on POD2 and 96.60 (17.4) mg/dl on POD3. In the control group, mean FBS was 86.96 (10.28) mg/dl on POD1, 88.81 (8.87) mg/dl on POD2 and 88.16 (8.50) mg/dl on
Pod3. Using the Mann-Whitney test, the fasting sugar values were found to be significantly higher than in the study group on POD1 ($P = 0.004$), POD2 ($P = 0.035$) and POD3 ($P = 0.001$).

Mean PPBS in the study group was found to be 139.16 (20.59) mg/dl on POD1, 138.17 (18.05) mg/dl on POD2 and 138.32 (15.10) mg/dl on POD3. Mean PPBS in the control group was 128.95 (10.52) mg/dl on POD1, 131.97 (9.68) mg/dl on POD2 and 130.88 (9.48) mg/dl on POD3.

Using the Mann-Whitney test, the postprandial blood sugar values were found to be significantly higher in the study group on POD 1 ($P = 0.001$) and POD3 ($P = 0.001$) [Figures 4 and 5].

There was a statistically significant positive correlation between pre-operative HbA1c and FBS on all days [POD1 ($r = 0.49, P = 0.000$), POD2 ($r = 0.51, P = 0.000$), POD3 ($r = 0.50, P = 0.000$)]. The pre-operative HbA1c also had a positive correlation with all the PPBS values [POD1 ($r = 0.49, P = 0.000$), POD2 ($r = 0.54, P = 0.000$) and POD3 ($r = 0.53, P = 0.000$)]. The correlations were moderate.

A strong correlation was found between FBS and PPBS on all three PODs [POD1 ($r = 0.81, P = 0.000$), POD2 ($r = 0.80, P = 0.000$), POD3 ($r = 0.76, P = 0.000$)]. A pairwise comparison of data showed that patients with higher preoperative FBS had significantly higher FBS on all three PODs in the study group ($P = 0.000$). In the control group, a similar effect was noted only on POD2 ($P = 0.000$) and POD3 ($P = 0.08$) However, there was only a moderate correlation between HbA1c and FBS/PPBS.

Patients who received dexamethasone had a steeper rise in mean blood glucose levels. This rise was statistically significant at all times and persisted for up to 72 hours. About 10.7% (8/75) of the patients who had received dexamethasone had blood glucose levels more than 180 mg/dl, requiring insulin. Though the fasting blood glucose and postprandial blood glucose ranges for three PODs were higher in the study group, they were within the normal range according to the American Diabetic Association criteria.[8] The results imply the possibility of clinically insignificant hyperglycaemia in diabetics/pre-diabetics following a single dose of steroid.
No significant differences were noted in the secondary outcomes. Mean analgesic consumption was 100.8 mg (7.44) in group A and 99.6 mg (5.02) in group B. A median of 40 and 0 was observed in the pain and PONV scores respectively in both groups. Mean hospital stay was 3.53 (0.50) and 3.55 (0.50) days in groups A and B, respectively.

**DISCUSSION**

Dhatariya K. highlighted the increased risk of developing insulin resistance and hyperglycaemia with the use of perioperative single-dose steroids such as dexamethasone. Bartlett et al. also emphasised the significant differences in blood glucose levels of non-diabetic patients receiving a single dose of dexamethasone. They observed a steeper rise in the mean blood glucose level, which was evident from the first post-operative day. Patients undergoing anaesthesia and surgery often show hyperglycaemic responses attributed to the stress-induced release of glucagon, epinephrine and cortisol.

The hyperglycaemia induced by dexamethasone was evidenced by the higher mean glucose values at all-time points, compared to the control group. The highest percentage increase from the baseline was 65% (maximum increase of 54.83 from baseline of 84.33 mg/dl) in the dexamethasone group and 52% (maximum increase of 57.53 from mean baseline sugar of 84.44 mg/dl) in the control group. The rise in blood sugar was statistically significant on all three days. The hyperglycaemia that occurred earlier, was higher and prolonged, despite the non-diabetic status of the patients. This was in contrast to the findings by Corcoran et al., who concluded that dexamethasone did not induce greater hyperglycaemia in non-diabetics and even in well-controlled diabetic patients.

In the current study, although greater glucose levels were noted in the intraoperative period, the rise in glucose levels was similar in both the groups (9.43 (4.1) mg/dl in the dexamethasone group versus 9.27 (4.4) mg/dl in placebo group). Maximum changes in glucose levels were identified on the first POD (14.71 (10.70) mg/dl in the dexamethasone group versus 2.52 (1.26) mg/dl in the placebo group). This can be explained by the low surgical stress in our population (as middle ear surgery is not a very invasive surgery). A study by Ali et al. showed a statistically significant increase in intraoperative blood glucose levels over a 4 h period in patients receiving a single dose of dexamethasone at the time of induction. Data similar to ours were reported by Tien et al. who studied the effect of dexamethasone given preoperatively on the blood glucose profiles of diabetic and non-diabetic patients. However, our findings differed from the findings of several authors who stated there was no evidence of the association between perioperative dexamethasone administration and higher blood glucose levels. Dexamethasone administration in patients undergoing arthroplasty increased postoperative hyperglycaemia during the first 24 to 72 hours. Another study by Bonilla et al. showed peak glucose levels in the first 24 hours. Our findings were different from both these studies. The blood glucose values performed 120 minutes after administration of dexamethasone/placebo were similar in both groups. However, our study group showed significant elevations in blood glucose levels, especially after 24 hours. This rise persisted for up to 72 hours, probably due to the long half-life of dexamethasone. Our findings were similar to those of a retrospective analysis by Herbst et al.

A large randomised controlled trial showed that even a single dose of dexamethasone significantly reduced the incidence of PONV. However, we found no significant difference in PONV scores, which might be attributed to the routine administration of ondansetron to all patients. Antiemetic properties of dexamethasone are due to its anti-inflammatory effect, direct central action at the solitary tract nucleus, interaction with serotonin and receptor proteins tachykinin NK1 and NK2 and alpha adrenaline, etc., maintenance of the normal physiological functions of organs and systems, regulation of the hypothalamic-pituitary-adrenal axis and by reducing pain and concomitant use of opioids. Despite the surge in blood sugar, we found no increase in infection or wound healing time. Also, there was no difference in LOS. However, our findings may be limited due to the type of surgery which has lesser tissue handling and thus less pain and a better recovery profile. Herbst et al. showed that perioperative steroids were associated with a 20% decrease in the LOS which may be due to reduced postoperative pain and nausea and subsequent reduced opioid requirements.

Perioperative hyperglycaemia occurs in 20–40% of post-surgical patients. Around 12–30% of these patients are non-diabetics before the surgery and anaesthesia. Of these, 30–60% develop impaired carbohydrate intolerance and 60% develop diabetes in one year. However, a single dose of dexamethasone
had minimal side effects and was not found to influence adrenocorticotropic hormone or cortisol secretion in the perioperative period.\cite{20,21}

Whilst there are data to show that dexamethasone use in the perioperative period raises blood glucose levels, there are almost no published data on the effects of this drug on postoperative morbidity and mortality in patients undergoing non-cardiac surgery.\cite{9}

The present study has two major strengths. The data was collected for 72 hours postoperatively, taking into account the duration of action of dexamethasone. The study population included only patients undergoing middle ear surgery, ensuring uniform surgical stress. However, the assessment of SSI ideally needs monitoring for up to 30 postoperative days.\cite{22}

The failure to derive inferences about SSI was a major limitation of our study. Only non-diabetics were included in this study. Hence, the effects of a single dose of steroid cannot be generalised to pre-diabetics or diabetics. We recommend that this area warrants further large-scale studies. Although steroid pre-treatment represents a potentially important biological modifier of perioperative inflammatory responses and organ dysfunction, a safe single dose of prophylactic perioperative dexamethasone is yet to be determined.

**CONCLUSION**

A single dose of dexamethasone given perioperatively produces a higher, earlier and prolonged increase in postoperative sugar levels in non-diabetic patients. The steeper and prolonged surges in blood sugar levels seen with even a single dose of dexamethasone indicate the need for prolonged monitoring and judicious dosing. Considering the dose-dependent relationship between hyperglycaemia and major postoperative complications, the administration of even a single dose of dexamethasone must be done with caution.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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