Effects of Single Dose of Dexamethasone on Perioperative Blood Glucose Levels in Patients Undergoing Surgery for Supratentorial Tumors – An Observational Study

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Abstract

Introduction: Dexamethasone is commonly administered in intracranial tumors to reduce the cerebral edema. Its administration may be associated with hyperglycemia. The primary objective of this study was to study the magnitude of rise in blood sugar levels following the administration of a single 10 mg dose of dexamethasone. Methods: Seventy patients who underwent various neurosurgical procedures were enrolled in the study. Group D (n = 35 undergoing surgery for intracranial tumors) were administered injection dexamethasone 10 mg while as Group P (n = 35 undergoing surgery for subarachnoid hemorrhage) received placebo. Blood samples were obtained through the arterial line at baseline (before dexamethasone administration), 60, 120, 180, and 240 min after the dexamethasone administration and blood glucose concentrations noted. Results: Glucose concentrations were significantly increased in patients who received dexamethasone compared with those who received placebo (P < 0.05). Blood glucose concentrations at different time intervals were greater when compared with the baseline blood sugar levels in both the placebo and dexamethasone group (P < 0.05). The arterial blood glucose concentration in those who received 10 mg dexamethasone (n = 35) increased from 95.29 ± 13.69 mg.dl⁻¹ to 139.97 ± 10.34 mg.dl⁻¹ over 4 h, compared with a change from 94.74 ± 10.05 mg.dl⁻¹ to 122.34 ± 10.68 mg.dl⁻¹ in those who received placebo (n = 35) (P < 0.05). Conclusion: The administration of a single intravenous dose of 10-mg dose dexamethasone caused a significant increase in the blood glucose concentrations at different point intervals when compared with the placebo over a 4-h period. We recommend intensive monitoring of the blood sugar levels during the intraoperative period to prevent the development of severe hyperglycemia and its associated complications.

Keywords: Dexamethasone, hyperglycemia, intracranial tumors

Introduction

Dexamethasone in low doses (10 mg) is commonly administered in intracranial tumors to reduce cerebral edema.[1] The preoperative and intraoperative administration of dexamethasone significantly reduces the vasogenic edema, causing a decrease in the mass effect and facilitating the surgical access to the intracranial tumor. It is also administered at the time of induction for the prevention of postoperative nausea and vomiting (PONV) after various surgical procedures. It may be used to reduce the pain induced by administering intravenous (i.v.) propofol at the time of induction of anesthesia.[2]

However, its administration may be associated with increased blood glucose levels by inducing hepatic gluconeogenesis and increasing insulin resistance.[3] Hyperglycemia can lead to cellular dehydration and osmotic diuresis, which may result in systemic hypovolemia, and alterations in the concentrations of various electrolytes.[4]

Lanier et al. found that blood glucose increases of 40 mg.dl⁻¹ were associated with a profound worsening of the postischemic state.[5]

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neurologic outcome in primates.\(^5\) In the setting of cerebral ischemia, it has been observed that in both animals and humans, the administration of corticosteroids will exacerbate brain injury due to increased blood glucose concentrations.\(^6\) The elevated blood glucose levels may lead to increased morbidity\(^7\) and worsened neurologic outcomes in intra- and post-operative period. Evidence suggests hyperglycemia is associated with worse outcomes in glioblastoma.\(^8\)–\(^10\)

The primary objective of this study was to study the magnitude of rise in blood sugar levels following the administration of a single 10 mg dose of dexamethasone.

A better control of hyperglycemia during the intra- and post-operative period may help in improving the outcome in patients who are at risk for neurologic ischemia.

**METHODS**

This study was conducted at a tertiary care hospital in northern India. Seventy patients who underwent various neurosurgical procedures were enrolled in the study. They were divided into two groups. Group D consisted of 35 adult patients with intracranial tumors, who were scheduled to undergo elective craniotomy and tumor decompression. They were administered injection dexamethasone 10 mg (2.5 ml) intravenously immediately after induction. Group P consisted of patients undergoing surgery for subarachnoid hemorrhage who received placebo (2.5 ml of normal saline).

Prior data\(^{11}\) indicated that the percent change in blood glucose from basal to peak level was 17% among controls and 53% in patients receiving dexamethasone injection in the perioperative period. Therefore we needed to study 26 cases and 26 controls to be able to reject the null hypothesis that the exposure rates for cases and controls are equal with probability (power) of 80% and an alpha error of 5%. To account for the loss of subjects or samples, we recruited one-third more cases, making the total sample size of 70; 35 cases and 35 controls.

Informed consent was taken from all the participants, after explaining the main objectives of the study and the possible complications associated with the surgical and anesthetic procedure. All patients were subjected to detailed clinical history and a complete general physical and systemic examination in the preoperative period. Routine investigations such as complete hemogram, kidney function tests (serum urea and serum creatinine), liver function tests (serum albumin, serum bilirubin, alkaline phosphatase, serum glutamic pyruvic transaminase serum glutamic oxaloacetic transaminase), urine examination, coagulation profile, electrocardiogram, and chest X-ray (posteroanterior view) were carried out in all patient.

None of the patients was administered any premedication. After establishing basic essential monitoring (electrocardiogram, HR, pulse oximetry, and capnography), anesthesia was induced in all patients with fentanyl 2 µg kg\(^{-1}\) and propofol 2 mg kg\(^{-1}\). Injection atracurium 0.5 mg kg\(^{-1}\) body weight was administered to facilitate endotracheal intubation. After endotracheal intubation, anesthesia was maintained with a mixture of oxygen and nitrous oxide with isoflurane. Atracurium was administered to maintain two twitches on the neuromuscular monitor. Isoflurane was administered at 1 minimum alveolar concentration till skin closure. After anesthetic induction and tracheal intubation, arterial line was inserted in radial or dorsalis pedis artery for monitoring invasive arterial blood pressure. Central line was inserted under ultrasound guidance in the right internal jugular vein for central venous pressure monitoring and administration of fluids and medications. Nasopharyngeal temperature, inhalational agent concentration, and neuromuscular monitoring were done using BeneView T5 monitor on Mindray Wato Ex-65 workstation. At skull pin insertion, 50 µg of injection fentanyl was administered to blunt the hemodynamic responses to skull pin insertion. Repeated doses of injection fentanyl µg kg\(^{-1}\) were administered every hourly till dural closure. IV paracetamol (1 g) was given to all the patients at the end of the surgery. At the end of the skin closure, the residual neuromuscular block was reversed using neostigmine 0.05 mg kg\(^{-1}\) and glycopyrrolate 0.02 mg kg\(^{-1}\). Patients were extubated when they were breathing spontaneously and were obeying commands.

Baseline blood glucose concentrations were quantified in arterial blood gas samples along with other parameters on the blood gas analysis by withdrawing 0.5-mL blood samples using a blood gas analyzer (Gem Premier 3000, Instrumentation laboratory company Bedford USA). All patients with intracranial tumors with vasogenic edema evident on neuroimaging received dexamethasone 10 mg volume (dexamethasone sodium phosphate, Cadila pharmaceuticals Ahmedabad India) as an i.v. bolus after induction of anesthesia. Patients undergoing surgery for subarachnoid hemorrhage received placebo in the form of 2.5 ml of normal saline. Blood samples were obtained through the arterial line at 60, 120, 180, and 240 min after the bolus and blood glucose concentrations were noted in arterial blood gas samples along with other parameters on the arterial blood gas analysis. All the data were analyzed by SPSS version 15.0. The data were noted as mean and SD The blood glucose concentrations taking time as a repeated factor was compared with the baseline blood sugars using independent samples test. The blood glucose levels between the two groups were compared at different time intervals were also compared. \(P < 0.05\) was considered statistically significant.

**RESULTS**

The demographics of subjects in both the dexamethasone and placebo groups were similar in terms of age (58 ± 15 compared to 57 ± 17, \(P > 0.05\)) and weight (61 ± 14 compared to 59 ± 16) as shown in Table 1. However, the nature of the underlying pathology and surgery was different in the two groups. Group P (dexamethasone group) consisted of subjects with subarachnoid aneurysmal hemorrhage for clipping whereas Group D consisted of subjects with intracranial tumors which received dexamethasone. All patients with
pituaria tumors were excluded from the study. The patients included in the placebo and control groups were receiving levetiracetam, phenytoin, or lacosamide as antiepileptic drugs. The baseline arterial blood glucose concentrations after the induction of anesthesia in the placebo group were between 75 and 119 mg.dL$^{-1}$ in the placebo group while as in the dexamethasone group the blood sugar levels varied between 77 and 123 in the placebo group. The mean ± SD of baseline blood sugar levels between the two groups was similar with $P > 0.05$ [Table 2]. That though there was no difference between the baseline glucose concentrations, at subsequent hourly time intervals, glucose concentrations were significantly increased in patients who received dexamethasone compared with those who received placebo [Table 2]. It was also observed that the blood glucose concentrations at different time intervals were greater than the baseline blood sugar levels in both the placebo and dexamethasone group [Table 2]. The area under the curve for blood glucose concentrations in patients receiving dexamethasone was more in patients receiving dexamethasone than those receiving placebo [Figures 1 and 2]. However, the time to the peak rise of blood glucose was similar (221.14 ± 43.10 in placebo versus 217.71 ± 41.38 in dexamethasone; $P > 0.05$) in both groups. It was observed that there was a 51.11% ± 17.42% increase in blood glucose levels in patients receiving dexamethasone while as in patients receiving placebo there was a 30.81% ± 13.57% increase in blood sugar levels. It was observed that in both the placebo and the dexamethasone groups the blood sugar levels at 60 min, 120 min, 180 min, and 240 min were increased when compared to the baseline blood glucose levels [Table 3].

### Discussion

Dexamethasone is a commonly used steroid with potent anti-inflammatory, analgesic, and antiemetic actions during the perioperative period. The Society for Ambulatory Anesthesia has recommended a dose of dexamethasone 4–5 mg for patients at high-risk for PONV.[12] Dexamethasone is widely used in the treatment of vasogenic edema in patients with mass effect with intracranial tumors. The administration of dexamethasone increases blood glucose concentrations mediated through the stimulation of hepatic gluconeogenesis and inhibition of glucose uptake by peripheral tissues.[13] The stress response following surgical trauma is accompanied by the release of stress hormones as glucagon, epinephrine, and cortisol which causes an increase in hepatic gluconeogenesis and glycogenolysis.[14,15] Schricker et al. observed that in patients who underwent hysterectomies (did not receive any intraoperative dose of steroids), there was an increase in glucose concentrations from a mean ± SD of 89 ± 21 mg.dL$^{-1}$ preoperatively to 148 ± 25 mg.dL$^{-1}$ 2 h after surgical closure.[16] This study emphasized the role of stress response in elevating the blood glucose levels in the absence of the administration of exogenous corticosteroids.

### Table 1: Demographics

| Group       | n  | Mean±SD (mg.dL$^{-1}$) | P     |
|-------------|----|------------------------|-------|
| Basal       | P  | 35                     | 94.74±10.05 | 0.85  |
|             | D  | 35                     | 95.29±13.69 |       |
| Time060     | P  | 35                     | 99.57±11.72 | 0.00**|
|             | D  | 35                     | 114.51±14.68|       |
| Time120     | P  | 35                     | 110.86±12.39| 0.00**|
|             | D  | 35                     | 128.89±11.10|       |
| Time180     | P  | 35                     | 114.80±9.49 | 0.00**|
|             | D  | 35                     | 133.74±9.25 |       |
| Time240     | P  | 35                     | 122.34±10.68| 0.00**|
|             | D  | 35                     | 139.97±10.34|       |
| Peak glucose| P  | 35                     | 123.17±10.83| 0.00**|
|             | D  | 35                     | 141.94±9.088|       |
| AUC         | P  | 35                     | 976.09±77.76| 0.00**|
|             | D  | 35                     | 1107.17±86.31|      |
| Time to peak glucose value (min) | P  | 35 | 221.14±43.10 | 0.74** |
|             | D  | 35                     | 217.71±41.38|       |
| Percent change| P  | 35 | 30.81±13.57 | 0.06  |
|             | D  | 35                     | 51.11±17.42 |       |

**P<0.05 compared to placebo glucose concentration at the corresponding time interval. P=Placebo; D=Dexamethasone, Time060=At 60 min after dexamethasone administration, Time120=At 120 min after dexamethasone administration, Time180=At 120 min after dexamethasone administration, Time240=at 240 min after dexamethasone administration, AUC=Area under curve, SD=Standard deviation.
A few studies have previously tried to study the effect of single low-dose IV dexamethasone on the incidence of perioperative hyperglycemia. Two nonrandomized studies were performed in a neurosurgical patient population. Pasternak et al. observed that patients who received a dose of 10 mg dexamethasone had increased intraoperative blood glucose concentrations (149 mg.dl\(^{-1}\)) than those who received placebo (103 mg.dl\(^{-1}\)). Lukins and Manninen also found, that in patients receiving dexamethasone (for reduction of cerebral edema in patients undergoing craniotomy) the peak blood sugar was much higher in patients receiving 14 mg dexamethasone (198 mg.dl\(^{-1}\)) compared with a peak blood sugar of 140 mg.dl\(^{-1}\) in those who did not receive it. In nonneurosurgical procedures, Hans et al. observed that there was a similar increase in blood glucose concentrations in both nondiabetic and type 2 diabetic patients who received 10 mg dexamethasone.

In this study, there was a lack of a control group, and it was unclear whether the intraoperative hyperglycemia was secondary to dexamethasone administration or due to catecholamine release due to the stress response to surgery. Nazar et al. observed that patients who received 8 mg dexamethasone had a higher maximum blood glucose concentrations (187 mg.dl\(^{-1}\)) compared with controls who did not receive steroids (158 mg.dl\(^{-1}\)). A major limitation of this study was the use of glucose-containing solutions in the intraoperative period, which could have caused the observed changes. A number of perioperative factors as age, sex, body weight, and preoperative medications influence the incidence of perioperative hyperglycemia.

In our study, the demographic profile (age and weight) was similar. The intraoperative anesthetic management was standardized and similar in both Group P and Group D. There was no use of dextrose containing fluids in the intraoperative period and only normal saline was used as a replacement fluid in all patients. As the type and duration of surgical procedure has a significant effect on the neuroendocrine response to surgery, an attempt was made to match the cases with similar controls. Hence, all subjects (receiving dexamethasone 10 mg undergoing craniotomy for intracranial tumors were compared with controls (receiving placebo) undergoing craniotomy for subarachnoid hemorrhage. This was an attempt to ensure that cases and controls are similar to each other as much as possible to eliminate the bias.

We observed from our study that the blood sugar levels increased progressively as the duration of the surgery progressed. It was observed that the rise in blood sugar levels was more in patients who received dexamethasone than the placebo group. The findings were similar to the findings observed by Pasternak et al. and Lukins and Manninen. Our study enrolled a higher number of patients than Pasternak et al. who studied 10 patients in each group, while as we studied 35 patients in each group. Our comparisons between the placebo and the interventional groups were more homogeneous. We compared only two groups, the group receiving dexamethasone was the being operated for intracranial tumors, while as the placebo group being operated for subarachnoid hemorrhage was not given any corticosteroid. This was in contrast to Pasternak et al. and Lukins and Manninen in whom the placebo group was heterogeneous (consisting of patients with intracranial aneurysm, arteriovenous malformation, seizure surgery, superficial temporal artery to middle cerebral artery anastomosis, etc.).
and microvascular decompression for trigeminal neuralgia). A uniform anesthetic technique was followed throughout the surgery for both groups in our study. This was in contrast to Pasternak et al.,[11] where nitrous oxide/narcotic-based technique was used intraoperatively for a short duration in 4 of the 10 cases in placebo group to facilitate intraoperative electrocorticography for seizure focus resection. This could have influenced the blood sugar levels in the placebo group. In our study, all patients were on three antiepileptic drugs (phenytoin, levetiracetam, and lacosamide) which do not have any appreciable effect on blood sugar levels. No patient was receiving gabapentin which has been reported to alter the serum glucose concentration.[21]

In our study, we found that the peak blood glucose concentration occurred 8–10 h after the induction of anesthesia whether the patients received dexamethasone in the intraoperative period (Group I), or preoperative period (Group P) or did not receive dexamethasone (Group N). They found a moderate positive correlation (r = 0.34) between the duration of surgery and peak blood glucose concentration and suggested that the longer the surgery takes, the more the stress response effect on blood glucose. We did not observe the blood glucose levels beyond 4 h, but we found that the blood glucose levels were increased significantly at 4 h in both placebo and dexamethasone groups suggesting that surgical stress response may have a significant effect on modulating blood sugar levels in addition to the effects of corticosteroids. Pasternak et al.[11] observed similar findings with a peak blood sugar levels of 149 mg.dl⁻¹ in the dexamethasone group attained at 4 h and 103–104 mg.dl⁻¹ attained at 3 and 4 h in the placebo group. The magnitude of the blood glucose increase in our study was not severe enough to result in neuronal injury or exacerbate the neuronal injury. The maximum blood sugar level observed in patients receiving dexamethasone was 158 mg.dl⁻¹ and in patients who did not receive dexamethasone, it was 143 mg.dl⁻¹. This increase was not >180 mg.dl⁻¹ which may be deleterious and exacerbate the neuronal injury.[22] The aim of this study was not to detect an outcome difference between patients who received dexamethasone and those who received placebo in terms of exacerbating neuronal injury; however, this study may be helpful in taking appropriate steps for the prevention of hyperglycemia-induced neuronal injury.

The study had several limitations. First, it was not a randomized controlled study. The patients in the two groups had different types of pathology with different types of surgery. This may have contributed to the varying blood glucose levels in the two groups. A randomized controlled trial will not be ethical as it is a reasonable standard to give corticosteroids for intracranial tumors and avoid it in arteriovenous malformation, aneurysm, or epilepsy surgery. The duration of surgery was not noted or compared between the two groups and could be a potentially confounding factor.

Only nondiabetic patients were included in our study. The diabetic patients were intensively treated with insulin for raised blood sugar levels. Hence, the results cannot be extrapolated to the diabetic population.

**Conclusion**

The administration of a single i.v. dose of 10-mg dose dexamethasone at the time of induction, in patients undergoing craniotomy and tumor decompression causes an increase in the blood glucose concentrations at different point intervals in the intraoperative period. This increase was statistically significant when compared with the placebo over a 4-h period. Although the increase in blood glucose was not severe enough to cause neuronal injury, we recommend intensive monitoring of the blood sugar levels during the intraoperative period to prevent the development of severe hyperglycemia and its associated complications.

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**Conflicts of interest**

There are no conflicts of interest.

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