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# Effect of Dexamethasone on Perioperative Blood Glucose in Patients Undergoing Craniotomy

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## Abstract

**Objectives:** To study blood glucose levels in elective neurosurgical patients between those who received preoperative dexamethasone and those who did not receive dexamethasone. To study the incidence of required treatment to correct blood glucose levels.

**Methods:** The prospective observational study was conducted in 255 patients undergoing an elective craniotomy from December 2015 through August 2017. They were categorized into two groups according to preoperative dexamethasone administration. The blood glucose level was classified into three levels as hypoglycemia (less than 80 mg/dL), normal (80-180 mg/dL), and hyperglycemia (more than 180 mg/dL).

**Results:** The 255 patients were classified into the dexamethasone group (158 patients) and the non-dexamethasone group (97 patients). Hypoglycemia and treatment requirements were significantly greater in the non-dexamethasone group than the patients who received dexamethasone preoperatively, 30% vs 6%, p<0.01. Within four hours after surgery and between eight to 24 hours after surgery, hyperglycemia was significantly high in the dexamethasone group, 24% vs. 12% (p 0.023) and 8% vs. 1% (p 0.014), respectively.

**Conclusion:** The incidence of abnormal blood glucose was high in neurosurgical patients. Frequent blood glucose monitoring is mandatory for proper management during the perioperative neurosurgery period.

**Keywords:** Dexamethasone; Blood Glucose; Craniotomy; Perioperative;

## Introduction

The effect of hyperglycemia on brain function is harmful as the brain is absolutely dependent on a continuous glucose supply [1]. The deleterious effects of hyperglycemia occur at the molecular level and in the clinical presentation. Hyperglycemia disrupts the integrity of the blood brain barrier (BBB) and worsens cerebral edema [2]. In the setting of pre-existing neurological injury, hyperglycemia decreases the ischemic threshold of neurons which could burden brain ischemia [3]. Clinically, hyperglycemia induces a hyperosmolar state and osmotic diuresis. The patients are at risk for hypovolemia, electrolyte imbalances, mental status changes, or seizures [1]. The stress-induced hyperglycemia refers to an increased level of the blood glucose response to insulin counter-regulatory hormones (cortisol, glucagon, epinephrine, growth hormone) and pro-inflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-alpha) [4,5]. Perioperative hyperglycemia is considered as one of the surgical stress responses to surgery. The blood glucose is markedly exaggerated in poorly controlled diabetes mellitus. Controlling blood glucose levels in neurosurgical patients results in a lower rate of craniotomy wound infections, shortened lengths of hospital stay, reduced hospital costs, and overall clinical outcomes [6,7].

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Dexamethasone is a glucocorticoid with minimal mineral corticoid effect. It is used to reduce the peritumoral vasogenic edema in the intracranial compartment. The beneficial effects at the molecular level, radiologic findings, and clinical symptoms occur within hours [8]. The mechanisms of action are promoting Ang-1, the blood-brain barrier (BBB) stabilizing factors and clearing the extracellular fluid into the ventricular system [9,10]. Dexamethasone down regulates vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), the angiogenic factors that lead to losing endothelial cell junctions in tumor blood vessels [11,12]. Although glucocorticoids have many potential beneficial effects, they have various systemic complications. The most common endocrine complication of dexamethasone is hyperglycemia. However, all of the complications are dose-related. Despite decreasing vasogenic edema of the tumor, a single 10-mg dose of dexamethasone administered in nondiabetic patients significantly increases the blood glucose concentrations over a four-hour period [13]. Monitoring of the blood glucose concentrations for at least 12 hours in all neurosurgical patients with newly administered dexamethasone was suggested [14]. The purpose of the present study was to compare the incidence of abnormal blood glucose levels in neurosurgical patients who received preoperative dexamethasone with patients who did not receive dexamethasone. The treatment episodes for hypoglycemia and hyperglycemia were compared.

## Methods

After approval from the Institutional Ethics Committee, 313 patients undergoing an elective craniotomy during December 2015 through August 2017 were recruited. The study design was a prospective observation. Dexamethasone was ordered exclusively by the neurosurgeon. The frequency of blood glucose measurements and the decision of treatment depended on the attending anesthesiologist, who was not involved in the study. Exclusion criteria were the patients younger than 18 years old, previously diagnosed diabetes mellitus, and without fasting overnight. Candidates who had the overall perioperative blood glucose measurements less than seven times or received additional corticosteroids during surgery were excluded. The anesthetic records and postoperative records of the remaining patients were reviewed.

Time points of measurement and blood glucose levels data were extracted. The seven time points of blood glucose measurement were the average blood glucose during each specific interval. T1 was the first obtained blood glucose before the surgery, T2 and T3 were the blood glucose measured in the first to the second hours and the third to the fourth hours of surgery, T4 was blood glucose measured before the end of surgery. T5 was the blood glucose obtained within the first four hours after surgery. T6 was the blood glucose obtained within the fourth to the eighth hour after surgery. T7 was the average of blood glucose measured during the eighth to the twenty-fourth hour after surgery.

Intra-arterial catheter placement to monitor blood pressure was performed in all neurosurgical patients. Arterial blood sampling was obtained intermittently during the intraoperative and postoperative period using a gluco-strip and a glucometer device. Anesthetic technique and anesthetic drugs were not controlled in this study. Anesthetic maintenance could be volatile-based in air: oxygen mixture or total intravenous anesthesia (TIVA) technique. The choice of intravenous fluid was managed solely by the attending anesthesiologist. The blood glucose levels were arbitrarily categorized into three groups, less than 80 mg/dL, 80-180 mg/dL, and more than 180 mg/dL as hypoglycemia, normoglycemia, and hyperglycemia, respectively [15].

The primary outcome was the incidence of abnormal blood glucose at any time point during the intraoperative and the first 24-hour postoperative periods among patients who received and did not receive dexamethasone. The secondary outcome was the episode of required treatment with dextrose solution or insulin in perioperative period.

## Statistical Analysis

The nominal data were presented as number and percentage, then Chi-square or Fisher's exact tests were used to assess statistical differences. Non-normally distributed BG values were presented as median with range and then the statistical difference between groups was tested with Mann-Whitney U test, and the difference related within the group was analyzed with Friedman test. Statistical Package for the Social Science, version 20 (SPSS 20, IBM, Armonk, NY, USA) was used to perform statistical analysis, with p-values < 0.05 considered statistically significant.

## Results

Among 313 patients, fifty-eight were excluded because of the incomplete perioperative blood glucose measurements. The remaining 255 patients were classified in the dexamethasone group (158 patients) and the non-dexamethasone group (97 patients). Within the dexamethasone group, 105 patients (67%) received dexamethasone in the 24-48 hours preoperatively, and the remainder received it 48-96 hours before surgery. Table 1 shows patient characteristics, Glasgow coma scale (GCS)

**Table 1:** Patient Characteristics

| Variables | Dexamethasone (n=158) | Non-Dexamethasone (n=97) | *P*-Value* |
|---|---|---|---|
| Age (Years) | 49 (42, 57) | 48 (32, 58) | 0.139† |
| Male Patients | 45 (28%) | 37 (38%) | 0.109 |
| Body Mass Index | 23.5 ± 3.91 | 23.2 ± 3.98 | 0.485‡ |
| Asa | | | **0.035** |
| • 1-2 | 150 (95%) | 85 (88%) | |
| • 3-4 | 8 (5%) | 12 (12%) | |
| Average GCS Score | 15 | 15 | 0.986† |
| Previous Steroid Use | | | 0.311 |
| • Yes | 12 (8%) | 11 (11%) | |
| • No | 146 (92%) | 86 (89%) | |
| Surgical Diagnosis | | | **0.000** |
| • Tumor | 153 (97%) | 59 (61%) | |
| • scular | 1 (0.6%) | 29 (30%) | |
| • Other | 4 (2.4%) | 9 (9%) | |
| Preoperative Fasting Time | | | 0.480 |
| • 8-12 | 69 (44%) | 38 (39%) | |
| • >12 Hours | 89 (56%) | 59 (61%) | |

| | | | |
|---|---|---|---|
| Preoperative Blood Glucose Test<br>• Yes<br>• No | 5 (3%)<br>153 (97%) | 1 (1%)<br>96 (99%) | 0.412§ |
| Anesthetic Technique<br>• TIVA<br>• Volatile<br>• Both | 98 (62%)<br>17 (11%)<br>43 (27%) | 61 (63%)<br>15 (15%)<br>21 (22%) | 0.405 |
| Operation Time | 270 (210, 360) | 270 (240, 360) | 0.467† |

* Unless stated otherwise, values determined by Chi-square test of proportion (Z test)

† Mann-Whitney U test, presented in mean and interquartile range (IQR)

‡ Independent t-test

*§ Fisher's exact test*

score, history of previous steroid use, and anesthetic technique. The distribution of American Society of Anesthesiology (ASA) classification and diagnosis were different between patients who received and did not receive dexamethasone. A significantly greater number of patients in dexamethasone group were diagnosed with a tumor, 97% versus 61%, p < 0.01.

There was no patients received dextrose-containing fluid as maintenance. Fluid with dextrose was administered only in patients who were diagnosed of hypoglycemia. The result in Table 2 showed that there were a high number of patients in whom hypoglycemia had been documented but not received dextrose. Those patients were followed up blood glucose within an hour later. The correction was done after the consecutive episodes of hypoglycemia. Some of them turned to normoglycemia or even hyperglycemia.

Table 2 shows the variation of abnormal blood glucose and the required treatment episodes at different time points. Before surgery, hypoglycemia and treatment requirement were significantly greater in non-dexamethasone group than the patients who receive dexamethasone preoperatively, 30% vs 6%, p<0.01. Within four hours after surgery and between the 8th to 24th hours after surgery, hyperglycemia was significantly higher in the dexamethasone group, 24% vs 12% (p 0.023) and 8% vs 1% (p 0.014), respectively. Hypoglycemia and the episode of dextrose requirements in non-dexamethasone group were higher than patients receiving dexamethasone. Unlike, hyperglycemia and insulin, treatments were greater in the dexamethasone group.

**Table 2:** Frequency of Patients with Perioperative Blood Glucose Levelsand Treatment Episodes

| Time | Dexamethasone (n=158) | | | | Non-Dexamethasone (n=97) | | | |
|---|---|---|---|---|---|---|---|---|
| | Hypo glycemia | Dextrose | Hyper glycemia | Insulin | Hypo glycemia | Dextrose | Hyperglycemia | Insulin |
| Before Surgery(T1) | 9 | 1 | 2 | 0 | 29 | 10 | 1 | 0 |
| 1st - 2nd Hr Of Surgery (T2) | 2 | 0 | 7 | 1 | 11 | 6 | 1 | 0 |
| 3rd- 4th Hr Of Surgery (T3) | 2 | 0 | 6 | 1 | 8 | 5 | 3 | 0 |
| Before Surgery End (T4) | 1 | 0 | 5 | 1 | 8 | 3 | 3 | 0 |
| 4 Hr After Surgery (T5) | 0 | 0 | 38 | 12 | 1 | 0 | 12 | 1 |
| 4th - 8th Hr After Surgery (T6) | 0 | 0 | 22 | 11 | 1 | 0 | 5 | 2 |
| 8th -24th Hr After Surgery (T7) | 0 | 0 | 13 | 2 | 0 | 0 | 1 | 0 |

Figure 1 shows the parallel columns of blood glucose level classified as hypoglycemia, normoglycemia, and hyperglycemia between the groups of dexamethasone and non-dexamethasone receiving patients. Gradually increase of blood glucose level was markedly noticed in both groups. However, the degree of blood glucose increments was greater in patients receiving dexamethasone.

Figure 2 shows the gradual, but significantly increased median blood glucose in both groups. Blood glucose obtained in the pre-surgical period was 113 mg/dl then rose to 147 mg/dl in the fourth hour after surgery, p<0.01, in the dexamethasone group. Similar findings were revealed in the non-dexamethasone group, 87 mg/dl to 139 mg/dl, p<0.01.

## Discussion

This study shows that preoperative dexamethasone in non-diabetic patients undergoing a craniotomy cause's significant increase of blood glucose during surgery and postoperative period. The incidence of hyperglycemia increased from approximately 5% during the operation to 24% in the 4-hours postoperatively. This finding supports a previous report by Pasternak et al [13]. The authors stated that a single dose of dexamethasone during craniotomy could significantly increase blood glucose over a four-hour period [13]. In spite of no dexamethasone administration, intraoperative hyperglycemia has been shown in patients undergoing elective craniotomy due to a hypermetabolic stress response [14,16]. In this study, the blood glucose levels increased over four hours of neurosurgery and rose in the first four hours postoperatively. A study with traumatic brain injured patients reported an incidence of hyperglycemia (defined as blood glucose>150mg/dl) of 45%, and severe hyperglycemia (blood glucose>200mg/dl) of 15% [17]. The reported incidences were diverse across previous studies, and depended on the levels of blood glucose defined as hypoglycemia, hyperglycemia, and severe hyperglycemia [18,19]. The results of this study affirmed the essential of frequent monitoring blood glucose level in neurosurgical patients. Certain anesthetic drugs have specific effects on blood glucose levels. Propofol attenuates the stress response, decreases cerebral metabolic rate of oxygen and glucose metabolism, but volatile anesthetics decrease insulin secretion and increase blood glucose levels [1,20,21]. In this study, similar ratios of patients in the dexamethasone and the non-dexamethasone groups received propofol-based TIVA technique.

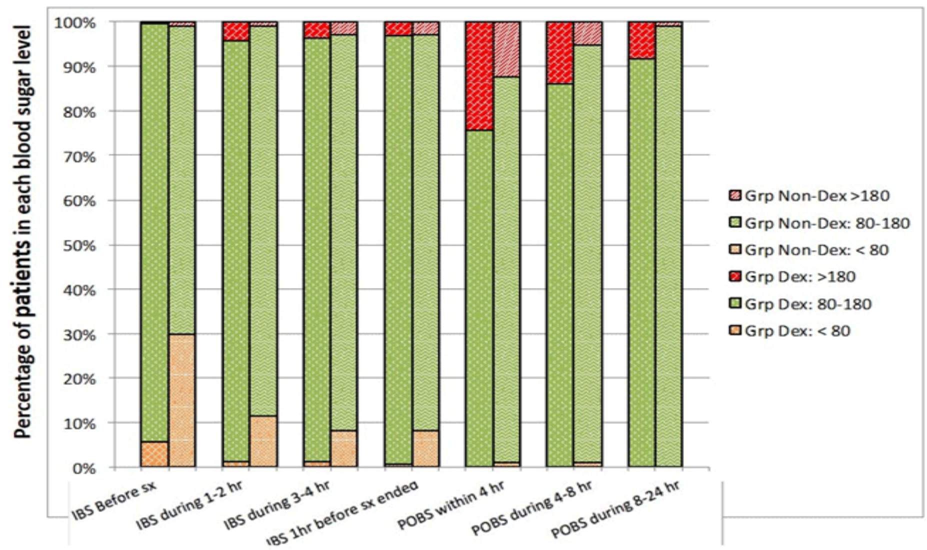


**Figure 1:** Percentage of patients in each blood glucose level (y axis)in group dexamethasone (Grp Dex): the first column of each pair, compared to group non-dexamethasone (Grp Non-DEX): the second column of each pair at different time intervals (x axis)
***Abbreviations: IBS:** intraoperative blood sugar, POBS: postoperative blood sugar*

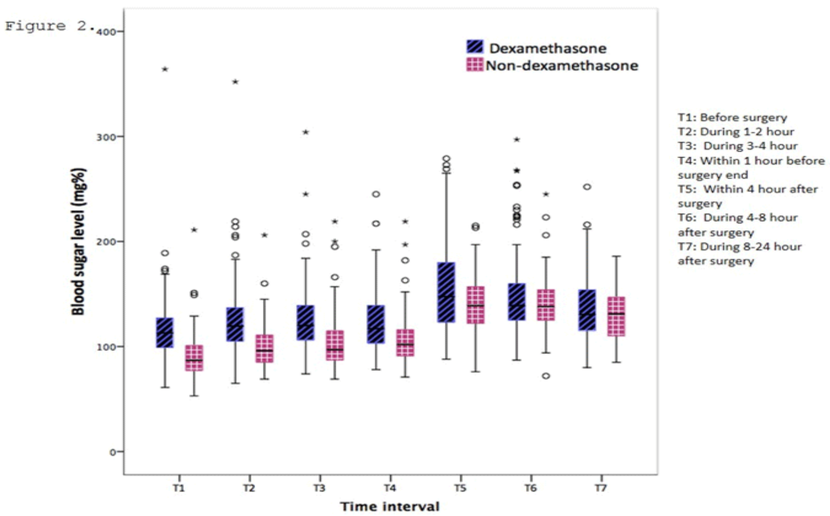


**Figure 2:** Box-plot diagramof blood glucose concentration ingroup dexamethasone, compared to group non-dexamethasone showing the median and the interquartile range and the outliers at different time intervals (x axis)

In clinical studies, hyperglycemia, defined with different blood glucose levels, have been associated with worsened neurologic outcomes after tumor resection (blood glucose > 180 mg/dL), TBI and other non-neurologic conditions e.g. neurocognitive dysfunction after coronary artery bypass graft surgery (blood glucose > 200 mg/dL) [22-24]. Currently, the optimal range of blood glucose levels was not clearly defined, a tight blood glucose control, range of 80-110 mg/dL, increases the risk of hypoglycemia. Hyperglycemia, defined as a mean glucose >140 mg/dl, and severe hyperglycemia, blood glucose >200 mg/dl, is associated with worsened neurologic results and increased mortality [25]. More realistically, the target blood glucose range of 108-180 mg/dL may be more appropriate in neurosurgical and neuro-critically ill patients [26].

Sharma D et al. explained that the concern of hypoglycemia caused a shortage of insulin administration during anesthesia, even when glucose values exceeded 200 mg/dL [27]. This study showed six patients with blood glucose exceeding 180 mg/dL. Only one of them received insulin infusion during surgery when the follow-up plasma glucose rose to 364 mg/dL. Although stress response hyperglycemia is common in neurosurgical patients, hypoglycemia still occurs and is usually under-recognized [28]. Therefore, blood glucose levels should be frequently checked in patients undergoing neurosurgery, not only the diabetes or steroid-receiving patients, but also to detect hypoglycemia in prolonged fasting patients without glucose-containing fluid infusion [29]. Otherwise 80 ml/hour of 5% dextrose solution should be given to prevent hypoglycemia [29]. This study found substantial hypoglycemia in non-dexamethasone patients compared to the other group (30% vs 6%). One-third of hypoglycemia patients were infused with 5% dextrose in 0.9% saline (5% D/NSS) solution during anesthetic maintenance, in rate of 1.5 ml/kg body weight. However, after the operation started, the occurrence of hypoglycemia decreased remarkably in both groups.

The limitations of this study include the definitive diagnosis of diabetes mellitus and the treatment effect, either dextrose infusion or insulin administration, to subsequent blood glucose levels. Some neurosurgical patients have unrecognized diabetes. To clearly diagnose diabetes mellitus, Hemoglobin A1C should be tested in patients who had a baseline blood glucose greater than 180 mg/dl. Moreover, no other stress hormones related to hyperglycemia were measured, so it was inconclusive whether dexamethasone was the only causative factor of hyperglycemia during perioperative craniotomy.

## Conclusion

Patients with preoperative dexamethasone administration incurred hyperglycemia during an elective craniotomy. Blood glucose level reached the highest point in the first four postoperative hours. The incidence of hypoglycemia was detected in non-dexamethasone, neurosurgical patients receiving dextrose-free solution. Therefore, frequent blood glucose monitoring is mandatory for proper management during the perioperative neurosurgery period.

## Ethics Approval

The study was approved by the Institutional Ethics Review Board, Faculty of Medicine, Chiang Mai University, with the study protocol number of ANE-2558-03463 and the Ethics number of 486/2558.

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