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**Original Research Article**

# Dexamethasone and Postoperative Capillary Glucose Levels in Type 2 Diabetes Mellitus

Elliza R[1] (✉), Nadia MN[1], Azlina M[1], Yeoh CN[1], Maryam B[1], Hanita O[2]

[1]Department of Anaesthesiology and Intensive Care, [2]Department of Diagnostic Laboratory Services, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia

**Abstract**

Perioperative intravenous (IV) dexamethasone is administered prophylactically for post operative nausea and vomiting. However, its glucocorticoid property which raises blood glucose is of concern, especially among diabetic patients. The surgical stress response also contributes to increased perioperative blood glucose. Prior studies showed higher glucose levels with dexamethasone 8 mg compared to 4 mg, hence we studied the effect of the lower dose amongst diabetic patients. This prospective, single blinded, randomised study recruited forty-six type 2 diabetes mellitus patients planned for surgery under general anaesthesia. They received IV dexamethasone 4 mg or saline (placebo) after induction of anaesthesia. Capillary blood glucose levels were recorded preoperatively, and subsequently at recovery ($T_0$), and at 6, 12, 18 and 24 ($T_6$, $T_{12}$, $T_{18}$, $T_{24}$) hours post-operatively. Median glucose levels were higher at 9.0 [10.5-7.7] mmol/l in the dexamethasone group, versus 7.4 [9.2-5.9] mmol/l in the placebo group at $T_0$, $p = 0.022$. Similarly at $T_6$, the dexamethasone group recorded higher glucose levels of 11.2 [15.0-9.3] mmol/l, versus 7.7 [9.0-6.2] mmol/l in the placebo group, $p = 0.001$. This corresponded to a significant difference between the groups, in the change of glucose levels from baseline values, $p = 0.042$. Subsequent readings at $T_{12}$, $T_{18}$, and $T_{24}$ were comparable between the groups. In conclusion, IV dexamethasone 4 mg in type 2 diabetic patients, resulted in higher glucose levels immediately postoperative and 6 hours later. The change in blood glucose from baseline levels was significant between the groups at 6 hours postoperatively. Glucose levels however remained within acceptable range of approved guidelines in both groups at all recorded intervals.

**Keywords:** capillary, dexamethasone, glucose, postoperative, type 2 diabetes mellitus

**Correspondence:**

Elliza Rusli. Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91455784 Fax: +603-91456585 Email: lizarusli@gmail.com

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## Introduction

Dexamethasone is administered to prevent postoperative nausea and vomiting (PONV). Although its mechanism of action as an antiemetic is not fully understood, it is widely used due to its efficacy and lower cost when compared to other antiemetic medications. The Consensus Guidelines for the Management of Postoperative Nausea and Vomiting recommends the administration of dexamethasone 4-5 mg intravenously (IV) after anaesthesia induction. However, one of the main concerns with dexamethasone is its glucocorticoid activity and the resultant perioperative hyperglycaemia, especially amongst diabetic patients (1).

Prior studies which investigated the effect of dexamethasone 8-10 mg showed increased postoperative glucose levels, more pronounced amongst diabetic than non-diabetic patients (2,3). Consequently, a lower dose of dexamethasone 4 mg was suggested as PONV prophylaxis in diabetic

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patients as it conferred the same antiemetic effect as dexamethasone 8 mg (4). Low et al. 2015 retrospectively investigated the effect of dexamethasone 4 mg versus 8 mg on postoperative glucose levels in type 2 diabetic patients and found higher glucose levels with the latter dose (5). There was no placebo group thus the increase in glucose levels secondary to dexamethasone could not be differentiated from that due to the surgical stress response.

## Materials and Methods

This was a prospective, single blind, randomised study which was carried out following approval from the Dissertation Committee of the Department of Anaesthesiology and Intensive Care Universiti Kebangsaan Malaysia Medical Centre (UKMMC), and the UKMMC Medical Research and Ethics Committee. Forty-six American Society of Anaesthesiologist (ASA) classification II patients, aged >18 years, with diabetes mellitus type 2 and preoperative capillary glucose ≤10 mmol/l, planned for surgery under general anaesthesia lasting less than four hours were recruited. Patients on perioperative steroid were excluded from this study. Written consent was obtained from the patients and all oral anti-diabetic medications were withheld on the morning of surgery as per institution's standard practice.

Patients were randomised by means of computer generated randomisation table into two groups; Group A received IV dexamethasone 4 mg (1 ml) and Group B received placebo (1 ml normal saline). The study drugs were prepared in 3 ml syringes by the anaesthetic trainees in-charge of the patients, and administered after induction of anaesthesia.

In the operating room, standard monitoring such as non-invasive blood pressure (NIBP), electrocardiograph (ECG), pulse oximetry ($SpO_2$) and end tidal capnograph were instituted. Induction of anaesthesia proceeded with IV fentanyl 2 mcg/kg and propofol 2 mg/kg. Neuromuscular blockade was left to the discretion of the attending anaesthetist, and if deemed necessary, IV rocuronium 0.6-1.0 mg/kg was administered. The airway was secured with either a supraglottic device or endotracheal tube. Anaesthesia was maintained with sevoflurane in an oxygen:air ratio of 1:1 with minimal alveolar concentration ranging 0.8-1.2. Intravenous dexamethasone 4 mg or placebo was administered after securing the airway. During the surgery, no dextrose containing IV infusion was given to the patient. Intravenous granisetron 1 mg was administered to patients as indicated. At the end of the surgery, IV neostigmine 2.5 mg and anticholinergics were given to reverse any neuromuscular blockade.

After extubation, the patient was sent to the recovery area where standard postoperative monitoring was instituted, and capillary glucose checked and recorded ($T_0$). Capillary glucose level was checked using the finger prick ACCU-CHECK Performa machines manufactured by ROCHE which were calibrated weekly by the nurses in-charge.

The ward staff nurses were instructed to record the patient's capillary glucose levels every 6 hours ($T_6$, $T_{12}$,

**Table 1**: Patient demography and perioperative surgical data. Values are shown as mean ± standard deviation, median [75$^{th}$-25$^{th}$ percentile] and number (percentage) where appropriate.

| | **Dexamethasone n=23** | **Placebo n=23** | ***p*-value** |
|---|---|---|---|
| Age (years) | 56.7 ± 11.4 | 62.1 ± 9.4 | 0.089 |
| Height (m) | 1.6 ± 0.1 | 1.6 ± 0.8 | 0.968 |
| Weight (kg) | 70.0 [77.0-62.5] | 64.6 [69.5-60] | 0.116 |
| BMI (kg/m$^2$) | 26.6 [30.2-23.9] | 25.2 [27.7-22.6] | 0.116 |
| Gender | | | 0.238 |
| Male | 9 (39.1) | 13 (56.5) | |
| Female | 14 (60.9) | 10 (43.5) | |
| Race | | | 0.549 |
| Malay | 13 (56.5) | 16 (69.6) | |
| Chinese | 7 (30.4) | 6 (26.1) | |
| Indian | 3 (13.0) | 1 (4.3) | |
| HbA1c (%) | 6.7 [8.1-6.1] | 6.5 [7.8-6.2] | 0.843 |
| Type of surgery | | | 0.254 |
| General surgery | 11 (47.8) | 8 (34.8) | |
| Urology | 2 (8.7) | 5 (21.7) | |
| Vascular surgery | 5 (21.7) | 2 (8.7) | |
| Orthopaedics | 2 (8.7) | 4 (17.4) | |
| ENT | 0 (0) | 1 (4.3) | |
| Ophthalmology | 3 (13.0) | 3 (13.0) | |
| Duration of surgery (min) | 115 [150-80] | 100 [140-45] | 0.448 |
| Duration before oral intake post-surgery (hours) | 3.5 [6.5-1.5] | 3.3 [4.5-2.0] | 0.422 |

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$T_{18}$, $T_{24}$) from $T_0$. The patient was followed up in the ward 24 hours postoperatively. The decision to commence oral intake was left to the surgeon's discretion. Insulin infusion was commenced if capillary glucose level was >10 mmol/l and omitted when capillary glucose was <10 mmol/l. Insulin was infused at 2, 3 and 4 units/hour when capillary glucose was 10-15 mmol/l, 15-20 mmol/l and >20 mmol/l respectively. Blood sample for serum HbA1c was drawn from patient and it was measured with Adam Arkray A1c HA 8180V analyser by a high performance liquid chromatography (HPLC).

Sample size calculation was carried out with α value set at 0.05 and power of study at 80%. Based on a study by Nazar et al. 2009, the difference in change in mean blood glucose levels pre and postoperatively, between patients who received dexamethasone versus placebo was 1.6 (9). Sample size was calculated from the 'Power and Sample Size Calculations'. The sample size calculated was 19 for each arm. Taking into account a 20% drop out rate, the total sample calculated was 46.

Data was analysed using the software IBM SPSS Statistic 20. Continuous data that was normally distributed was analysed using the independent t-test, and Mann-Whitney U was used to analyse continuous data not normally distributed. Intra-group analysis was done using the Wilcoxon Signed Rank Test with Bonferroni correction, where $p<0.01$ was regarded as statistically significant. Categorical data was analysed with the chi-square test with $p<0.05$ regarded as statistically significant.

## Results

There was no significant difference between the groups in terms of patient demography, baseline HbA1c and perioperative surgical data as depicted in Table 1. Dextrose 5% IV fluid was given preoperatively to 2 patients (8.7%) in the dexamethasone group and 1 patient (4.3%) in the placebo group, p=1.000. The amount administered was negligible and not statistically significant between the groups, p=0.590. Preoperative insulin infusion was commenced in 2 patients (8.7%) in the dexamethasone group and 1 patient (4.3%) in the placebo group, p=1.000. Postoperatively, 5 patients (21.7%) in the dexamethasone group and 8 patients (34.8%) in the placebo group required insulin infusion, p=0.326. The amount of insulin administered to the patients preoperatively and postoperatively was negligible, p=0.538 and p=0.313 respectively. There was no difference between the groups in surgical duration and mean duration before commencement of oral intake postoperatively.

**Table 2**: Capillary blood glucose. Values are shown as median [75th-25th percentile]

| Capillary blood glucose (mmol/l) at recorded times | Dexamethasone n=23 | Placebo n=23 | *p*-value |
|---|---|---|---|
| Baseline | 6.7 [8.1-5.2] | 5.9 [6.9-4.6] | 0.111 |
| $T_o$ | 9.0 [10.5-7.7][a] | 7.4 [9.2-5.9][b] | 0.022* |
| $T_6$ | 11.2 [15.0-9.3][a] | 7.7 [9.0-6.2][b] | 0.001* |
| $T_{12}$ | 8.9 [13.1-6.7][a] | 8.1 [10.2-6.5][b] | 0.170 |
| $T_{18}$ | 7.3 [10.0-6.4] | 8.0 [10.0-6.5][b] | 0.835 |
| $T_{24}$ | 9.0 [12.4-6.0] | 7.8 [10.3-6.7][b] | 0.676 |

[a]p<0.01(Bonferroni correction) when compared to baseline capillary glucose levels in group dexamethasone 4mg
[b]p<0.01 (Bonferroni correction) when compared to baseline capillary glucose levels in group placebo
*p<0.05 comparing dexamethasone 4mg and placebo group

Baseline preoperative capillary blood glucose level was comparable between the groups as shown in Table 2. However, capillary glucose levels were higher in the dexamethasone group at the recovery area ($T_0$), p=0.022, and at six hours postoperatively ($T_6$), p=0.001.

**Table 3**: Change in capillary glucose levels from baseline values. Values expressed as median [75th- 25th percentile]

| Capillary blood glucose (mmol/l) at recorded times | Dexamethasone n=23 | Placebo n=23 | *p*-value |
|---|---|---|---|
| $T_o$ | 2.8 [4.7-1.1] | 1.6 [3.1-0.2] | 0.091 |
| $T_6$ | 4.7 [8.1-0.4] | 1.7 [4.2-0.4] | 0.042* |
| $T_{12}$ | 1.9 [7.5- -1] | 2.2 [3.7-0.3] | 0.709 |
| $T_{18}$ | 0.5 [4.8-0.9] | 2.2 [4.6-0.3] | 0.108 |
| $T_{24}$ | 0.8 [6.1-0.2] | 2.4 [5.2-0.3] | 0.517 |

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Capillary glucose levels within the dexamethasone group increased from baseline values at $T_0$, $T_6$ and $T_{12}$ hours postoperatively. The placebo group showed significant increase in capillary glucose from baseline values at all recorded times. The difference in capillary blood glucose from baseline levels was significant between the groups at 6 hours postoperatively as shown in Table 3.

**Discussion**

Dexamethasone 8-10 mg administered for prophylactic PONV increased postoperative blood glucose, more so amongst diabetic patients (2,3). Higher postoperative blood glucose was observed amongst diabetic patients given dexamethasone 8 mg, when compared to dexamethasone 4 mg (4). We compared dexamethasone 4 mg against no dexamethasone to see if the former significantly increased baseline blood glucose levels, and to what extent any rise in postoperative glucose levels may have been attributed to surgical stress alone. We presumed that any rise in postoperative glucose would have been contributed by dexamethasone, or the surgical stress response in the placebo arm, as other confounders such as intra and postoperative infusions of dextrose containing solutions which may impact on blood glucose levels were eliminated. A prior study showed significant increase in blood glucose levels from median baseline values ranging 5.2 to 5.7 mmol/l, to a maximum median range of 7.8 to 9.0 mmol/l, $p<0.001$, amongst non-diabetic patients given perioperative dexamethasone 4 mg compared to those given saline. However, blood glucose levels did not differ significantly between the groups (6).

In our study, both groups had borderline controlled diabetes based on their HbA1c levels, and preoperative capillary blood glucose levels. On the initial postoperative assessment at the recovery area ($T_0$), capillary blood glucose was significantly higher in the dexamethasone than the placebo group. Mean surgical duration in the dexamethasone group was 115 minutes, comparable to that in the control group. This surgical duration closely corresponds to the point of maximum glucose level (2) and maximum plasma level of dexamethasone seen in prior studies (7), which was approximately two hours after the start of surgery, with higher glucose levels observed in the dexamethasone group (2,7). Dexamethasone is a glucocorticoid which acts on the intracellular receptor and mediates its effects through gene transcription. Consequently, its onset is slow, ranging 1-2 hours after administration, which may account for the raised glucose level observed at $T_0$ after dexamethasone administration (8).
The difference in capillary blood glucose from baseline levels was significant between the groups at 6 hours ($T_6$) postoperatively and capillary blood glucose was higher in the dexamethasone group. The median duration before oral intake was comparable between the groups at 3.5 (6.5-1.5) and 3.3 (4.5-2.0) hours for the dexamethasone and placebo groups respectively. The higher glucose level in the dexamethasone group could be contributed by oral intake in addition to the glycaemic effect of dexamethasone. Nazar et al. 2009 similarly found higher glucose levels in their dexamethasone group compared to the placebo group, from the $6^{th}$ to $12^{th}$ hour postoperatively (9). In our study, the difference in increase was significant even at $T_0$, and this may be due to our study population who were diabetic as opposed to Nazar et al's, who were of impaired glucose tolerance.

Subsequent capillary glucose levels at 12, 18 and 24 hours postoperatively showed no difference between the groups. This could be explained by the reducing plasma concentration of dexamethasone as the half-life of dexamethasone is 3.53 hours (10). At 24 hours postoperatively, 16 of the 46 patients (34.8%) had capillary glucose levels above 10.0 mmol/l, with the highest recorded at 15.8 mmol/l from the placebo group. Of the 16 patients, 6 (13.0%) were from the placebo and 10 (21.7%) from the dexamethasone arms. Toth et al. 1999 found that dexamethasone level was not detectable 24 hours after oral or intravenous administration (11), although the duration of action of dexamethasone is 72 hours (12). This may account for the increased glucose levels at 24 hours, or may be the result of the ongoing stress response. It is difficult to determine the magnitude of the stress response and its duration, thus predict when patient physiology would normalise to preoperative levels. The degree of hyperglycaemia signifies the extent of tissue injury and degree of surgical stimulus (13). Inadequate postoperative analgesia would further prolong the stress response with neuroendocrine effects persisting hence affecting homeostasis of glucose resulting in hyperglycaemia (14).

Dexamethasone 4 mg did not cause excessively high capillary glucose levels in patients with well controlled diabetes, and postoperative glucose levels were within acceptable range of approved guidelines (15).

**Study Limitation**

The limitation of this study was the heterogeneity in the type of surgeries, with different levels of surgical stimulus resulting in various levels of the surgical stress response. The surgical stress response triggers the release of catecholamines, growth hormone and cortisol secretions at different degrees, thus have varying impact on postoperative capillary glucose levels

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(13,16). Secondly, the studied population was amongst well controlled diabetic patients hence the results cannot be extrapolated to patients with uncontrolled diabetes. We selected patients with borderline controlled diabetes as we did not want to risk postoperative complications which may arise with the administration of dexamethasone in patients with poorly controlled diabetes. Finally, in our study, we did not standardise the method of securing the airway. According to Carron et al. 2012, the insertion of the Proseal™ laryngeal mask airway resulted in a lower stress response when compared to endotracheal intubation (17). This may have confounded our results.

## Conclusion

A single dose of IV dexamethasone 4 mg as PONV prophylaxis in patients with borderline controlled type 2 diabetes resulted in higher capillary glucose level at the immediate postoperative period and 6 hours later. The change in capillary blood glucose from baseline levels was significant between the groups at 6 hours postoperatively. Capillary blood glucose levels were within acceptable range of approved guidelines in both groups at all recorded intervals.

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