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Effect of Single Dose of Dexamethasone on Peri Operative Blood Glucose Levels in Non-Diabetic Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Laparoscopic cholecystectomy is associated with an increased risk of postoperative nausea and vomiting. Dexamethasone, a potent corticosteroid has antiemetic, analgesic action. A single dose increases blood glucose levels even in non-diabetics. We estimated perioperative blood glucose levels after the administration of 8 mg intravenous dexamethasone in non-diabetic patients undergoing laparoscopic cholecystectomy. Ethical committee approval and informed written consent were obtained from all 70 patients in this prospective randomized study. Two groups of 35 patients each received 8 mg intravenous dexamethasone or saline at induction and underwent laparoscopic cholecystectomy. Capillary blood glucose was measured at baseline and 1, 2, 4 and 6 hours. Diabetic patients were excluded. Statistical analysis was done using measures dispersion, Mann Whitney U test and Friedman's test. Demographic data, ASA status, type of surgery and duration of anaesthesia were comparable between both groups. In our study, after administration of 8 mg I.V. dexamethasone at induction, blood glucose levels increased from baseline (mean=87.5±7.8), peaked at 2 hours (mean=134.7±19.9), up to 6 hours (mean=127.6±13.8) in Group D while in Group S the mean glucose levels gradually increased from T0 (mean=84.9±8.9) to T6 (mean=110.9±16). When non-diabetic patients undergoing laparoscopic cholecystectomy are administered a single dose of 8 mg intravenous dexamethasone at induction of general anaesthesia, the blood glucose levels rise at various points throughout the perioperative period. This rise was within a range that was clinically acceptable and was not substantial enough to have an adverse effect that was clinically evident.

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Key Words
Dexamethasone, laparoscopic cholecystectomy, blood glucose, general anaesthesia

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INTRODUCTION

Laparoscopic cholecystectomy, a commonly performed elective surgical procedure is associated with a modestly increased risk of postoperative nausea and vomiting (PONV)[1]. Without treatment, PONV occurs in 20-30% of surgical patients[2]. It delays recovery due to complications like wound dehiscence, aspiration, dehydration and raised intracranial pressure[3].

Dexamethasone is a potent corticosteroid with antiemetic and analgesic action useful for PONV prophylaxis. It reduces the opioid requirement, alleviating the risk of PONV[4]. Dexamethasone has anti-inflammatory and immunomodulation effects, attenuates postoperative pain, improves mood and appetite and reduces the incidence and severity of sore throat following endotracheal intubation[1]. Preoperative dexamethasone reduces fatigue and improves the quality of recovery during the first 24 hours post-surgery. Hence, a single dose is recommended for routine use in patients undergoing laparoscopic cholecystectomy.

Single-dose of dexamethasone is however known to increase blood glucose levels in the perioperative period even in non-diabetics[5]. Hyperglycemia in the peri-operative period can cause dehydration, fluid shifts, electrolyte abnormalities, ketoacidosis and hyperosmolar states. It impairs leukocyte function and wound healing; these are worse with blood glucose surges rather than sustained hyperglycaemia. Although dexamethasone is known to have beneficial effects, there is some reluctance to use it due to the fear of hyperglycaemia.

The extent to which steroids affect perioperative blood glucose levels remains controversial[6]. Hence, we designed a study to look into the perioperative blood glucose variations, after administering dexamethasone in non-diabetics undergoing laparoscopic cholecystectomy, under general anaesthesia.

Aims and Objective: To estimate the perioperative blood glucose levels after administration of 8 mg intravenous dexamethasone in non-diabetic patients undergoing laparoscopic cholecystectomy under general anaesthesia.

MATERIALS AND METHODS

A Prospective randomized double-blind study was conducted between March 2021 and August 2022 at ESIC Medical College and PGIMSR, Rajajinagar, Bangalore.

A minimum of 30 patients were required in each group to detect an effect size of 0.9, considering a mean difference of 32.28 mg/dl in the blood glucose levels from pre-induction to the peak levels attained (based on the previous study conducted by Gülmez[7] to achieve a power of 90% and alpha error of 5%. To compensate for potential dropouts, a total of 35 patients were included in each group. Sample size is calculated using G*Power 3.1.9.7 software.

Following approval from institutional ethics committee, written informed consent was obtained in patients of either gender, aged between 18 years-60 years, undergoing elective laparoscopic cholecystectomy under general anaesthesia. They belonged to ASA physical status I or II, with BMI between 20-30 kg/m2.

We excluded patients with history of diabetes mellitus, pre-operative fasting blood glucose=100 mg/dl, HbA1c=5.7%. (As per American Diabetes Association diagnostic criteria for diabetes mellitus), known allergy to dexamethasone, patients who have received inhalational/oral/parenteral steroid in the last 48 hours or administered any medication altering blood glucose like OHA/glucose/vasoactive drugs, patients with a history of chemotherapy/radiotherapy within last 6 months, immunosuppressed patients and pregnant women.

Methodology: A detailed pre-anesthetic check-up including relevant blood investigations was done one day before the surgery. Fasting of 8 hours for solids and 2 hours for clear liquids was ensured.

All the patients were randomized into two groups using computer generated random number table.

Group D: Received a single dose of 8 mg in 5ml intravenous dexamethasone after induction of anaesthesia.

Group S: (Control group) received 5ml of normal saline. The study drug was prepared by an anaesthesiology resident (observer 1) who was not involved further in the study. Patients, anaesthesiologists involved in intraoperative care and investigators collecting postoperative data were blinded to patient group allocation.

On the morning of surgery, venous access was established and normal saline infusion instituted. Standard monitors were established. Anaesthesia was induced by intravenous midazolam 0.02 mg/kg, fentanyl 2 mcg/kg, propofol 2 mg/kg, vecuronium 0.15 mg/kg. Trachea was intubated with an appropriately sized endotracheal tube and anaesthesia was maintained with 35% oxygen, 65% nitrous oxide and 1-2% sevoflurane using positive pressure ventilation.

Laparoscopic cholecystectomy was performed by standard approach maintaining intra-abdominal pressure <14 mmHg during pneumoperitoneum. All patients were given intravenous 4 mg ondansetron, 75 mg diclofenac infusion and 1g paracetamol infusion 30 minutes before emergence from anesthesia. Residual neuromuscular block was reversed using neostigmine 50 mcg/kg and glycopyrrolate 1 mcg/kg. Trachea was extubated when the patient was awake.

Baseline finger-prick capillary blood glucose was measured just before the study drug administration i.e. baseline (T0) and at one hour (T1), two hours (T2), four hours (T4) and 6 hours (T6) post administration of study drug, using the same glucometer (Accu-Chek® Active Roche Diagnostics GmbH, Mannheim, Germany).

Postoperatively, dextrose-free IV fluids at 2 ml/kg/hour were infused for 6 hours. No dextrose-containing solution was given during the study. Postoperatively, fasting was maintained for 6 hours. Intergroup and intra-group comparison of blood glucose was made at each time and peak blood glucose level was noted for each patient to study the variation from baseline (pre-induction). Observations were documented as per the proforma.

Statistical Analysis: All the data collected were entered in a Microsoft Excel worksheet and analyzed using the statistical software SPSS 20.0. The Qualitative characters like were expressed in frequency with proportions and continuous study variables using descriptive statistics like Mean with SD and Median.

Study variables were tested for normality, using the Shapiro-Wilk test and data was found to be non-normal hence non-parametric tests are applied.

To compare study variables between any groups Mann-Whitney U-Test is applied and to assess the blood glucose level variation at different time interval Friedman Test is applied. To compare the change in glucose level from baseline at different time intervals Wilcoxon Signed Ranks Test is applied. If the p-value was<0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. All the patients completed the study without any complications and dropouts.

RESULTS AND DISCUSSIONS

Patient characteristics like age, gender distribution, co-morbidity status, BMI, duration of anesthesia and ASA status have been represented in Table 1.

Group D had 11.4% (4) co-morbidity of which 3 were hypertension and 1 was epilepsy. Group S had 17.1% (6) co-morbidity and all 6 were hypertension. All the surgeries were LC in both Groups. The HbA1C was in the normal range (<5.7%) with a range (4.0-5.6) in both Groups.

The Median blood glucose was compared in Group D and Group S at Baseline T0, T1, T2, T4, T6. At T1, T2, T4, T6, there was a statistically significant difference in blood glucose between the groups (T1-T6) with p-value of 0.000 (<0.05). At T0, there was no statistically significant difference in blood glucose between both groups. (p value=0.228). (Table 2, Fig. 1)

The change in blood glucose from T0-T6 is assessed in Group D and S. In Group D, the blood glucose at T2 was the highest compared to another time interval. There was a statistically significant difference in blood glucose levels at different time intervals p=0.000 (<0.05). In group S the blood glucose at T6 was the highest compared to another time interval. There was a statistically significant difference in blood glucose levels at different time intervals p=0.000 (<0.05). (Table 3)

In Group D and Group S the change in blood glucose from baseline to T1, T2, T4 and T6 was assessed. In group D all the 35 study subjects had increased blood glucose when compared to baseline. There was a statistically significant change in blood glucose compared to baseline with p<0.05. In Group S, most of the study subjects 97.1% had increased blood glucose when compared to baseline. There was a statistically significant change in blood glucose compared to baseline with p<0.05. (Table 4, Fig. 2)

Laparoscopic cholecystectomy being a minimally invasive surgery is associated with the risk of postoperative nausea and vomiting. Hyperglycemia during the perioperative period when a single dose of dexamethasone is prophylactically used has been a concern among clinicians even in non-diabetic patients. There are an increasing number of reports about positive effects from pre-operative single intravenous dose of 8 mg dexamethasone as a part of a multimodal pain and antiemetic strategy in conjunction with cholecystectomy[8].

In our prospective, randomized, double-blind study, we examined the effect of a single dose of 8 mg IV dexamethasone on perioperative blood glucose levels. The demographic profile (age, sex, BMI, ASA status, HbA1C) were comparable.

The intraoperative anaesthetic management was standardized in both groups. We did not use dextrose-containing fluids in the peri-operative period of up to 6 hours. As the type of surgery has a significant effect on the neuroendocrine response to stress, the cases were matched with controls.

The glucometers were also routinely calibrated every 24 hours according to our institutional guidelines in order to minimize any potential inaccuracies. We excluded ASA status >2 to avoid erratic glucose changes. Hence our results cannot be extrapolated to poorly optimized co-morbid patients.

In our study, blood glucose levels increased from baseline (mean=87.5±7.8), peaked at 2 hours (mean=134.7±19.9), up to 6 hours (mean=127.6±13.8) in Group D while in Group S the mean glucose levels gradually increased from T0 (mean=84.9±8.9) to T6 (mean=110.9±16). This pattern of intraoperative glucose levels resembled the studies conducted by Abdelmalak[9] Murphy[1] and Hans[10].

Although Hans *et al.* attributed hyperglycemia to the administration of 10 mg of dexamethasone at induction; they did not exclude the possibility that a hyperglycemic stress response was the cause. Pasternak[11] observed that patients who received a dose of 10 mg dexamethasone had increased intraoperative blood glucose concentrations (149 mg/dl) than those who received a placebo (103 mg/dl). Hans[10] observed that there was a similar increase in blood glucose levels in both non-diabetic and type 2 diabetic patients who received 10 mg of 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. In our study, since we have standardized the surgical procedure and it is a minimally invasive surgery, the risk of surgical stress response causing hyperglycemia is minimized. The presence of a control group helps us compare the response to surgical stress. Nazar[2] observed that patients who received 8 mg dexamethasone had higher maximum blood glucose levels compared with controls who did not receive steroids. A major limitation of this study was the use of glucose-containing solutions in the intraoperative period, which could have caused the observed changes.

In our study, 8 mg dose of dexamethasone moderately augmented the hyperglycemic response to surgery in patients without diabetes. The hyperglycemic effect of dexamethasone in diabetic patients who have either absolute insulin deficiency (Type 1 DM) or relative insulin deficiency with insulin resistance (Type 2 DM) cannot be predicted is expected to have limited ability to adjust for the dexamethasone-induced hyperglycemic effect.

In our study, there were no episodes of perioperative hyperglycemic episodes (>180mg/dl). Abdelmalak[9] in their study defined perioperative hyperglycemic episodes as blood glucose measurement >180 mg/dl. Consensus statements and reviews in ambulatory diabetic patients, inpatient diabetic patients and nondiabetic surgical patients have concluded that intraoperative blood glucose levels should be targeted at <180 mg/dL[1].

Tight peri-operative glycaemic control (<110 mg/dl) carries an increased risk of hypoglycemia (<70 mg/dl) and might be associated with increased morbidity and mortality. On the other hand, severe hyperglycaemia (>180mg/dl) may be associated with an increase in surgical wound infections, impaired wound healing and greater morbidity and mortality. Therefore, current recommendations are to aim for target blood glucose of140-180 mg/dl in the perioperative period[12].

The administration of dexamethasone increases blood glucose concentrations mediated through the stimulation of hepatic gluconeogenesis and inhibition of glucose uptake by peripheral tissues. 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[13].

Schricker[12] in his study emphasized the role of stress response in elevating blood glucose levels in the absence of the administration of exogenous corticosteroids.

In our study, since we have standardized the surgical procedure and it is a minimally invasive surgery, the component of surgical stress is minimized. The presence of a control group helps us compare the response to surgical stress.

We chose to exclude pre-diabetic and diabetic patients with poor glycemic control on the grounds of safety. They may be older and with multiple comorbidities. As this group of patients is more likely to demonstrate end-organ complications of diabetes and be more vulnerable to severe peri-operative hyperglycemia. Also, there are fewer studies done on non-diabetic patients as one would take interest in monitoring glucose levels in diabetic patients and it is unlikely that one would expect non-diabetic patients to exhibit hyperglycaemia.

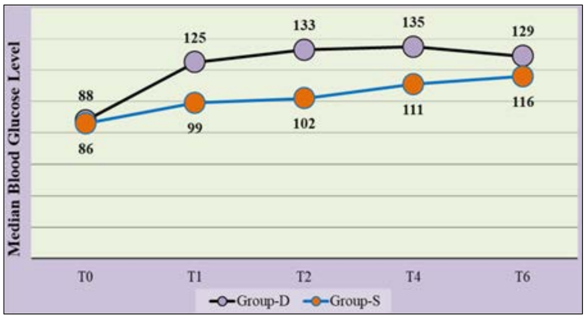

Fig 1: Comparison of blood glucose at different timing among the groups

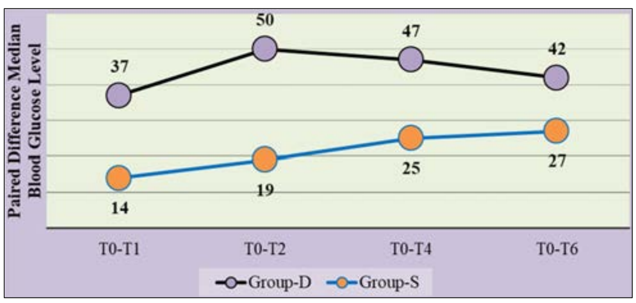

Fig 2: Comparison of Blood Glucose from baseline to different timings among Group D and Group S

Table 1: Patient Characterstics in both groups

Patient Characteristics	Group D	Group S	p-value
N	35	35	
Age (median)	39 years	38 years	0.374
Male/ Female	24/ 11	21/ 14	
Comorbidity	11.4% (4)	17.1% (6)	
BMI (median)	21.8 (20.9- 23.4)	21.5 (20.3- 23.3)	0.365
Duration of anesthesia (mean ±SD)	40.2 ±7	38.0 ±7	0.620
ASA status	ASA I: 80% (28)	ASA I: 85.7% (30)	
	ASA II: 20% (7)	ASA II: 14.3% (5)	

Table 2: Comparison of Blood Glucose at different timing among the groups

	Mean ± SD	Median	Mann-Whitney U	p-value
Baseline-T0				
Group-D	87.5±7.8	88.0	510.0	0.228
Group-S	84.9±8.9	86.0		
	`	T1		
Group-D	123.3±18.1	125.0	185.0	0.000
Group-S	98.8±13.6	99.0		
		T2		
Group-D	134.7±19.9	133.0	131.0	0.000
Group-S	104.1±14.7	102.0		
		T4		
Group-D	132.1±14.2	135.0	157.5	0.000
Group-S	109.1±15.6	111.0		
		T6		
Group-D	127.6±13.8	129.0	255.5	0.000026
Group-S	110.9±16.0	116.0		

Table 3: Assessment of Blood Glucose from baseline T0 to T6 in both Group D and S

Group D	Mean ±SD	Median	Friedman Test	p-value
T0	87.5±7.8	88	92.689	0
T1	123.3±18.1	125		
T2	134.7±19.9	133		
T4	132.1±14.2	135		
T6	127.6±13.8	129		
Group S	**Mean ±SD**	**Median**	**Friedman Test**	**p-value**
T0	84.9±8.9	86	102.134	0
T1	98.8±13.6	99		
T2	104.1±14.7	102		
T4	109.1±15.6	111		
T6	110.9±16.0	116		

Table 4: Comparison of Blood Glucose from baseline to different timings among Group D and Group S

Time	Paired Differences		Blood Glucose from baseline			Wilcoxon Signed	
	Mean ±SD	Median	Decreased n(%)	Increased n(%)	Constant n(%)	Ranks Test	p-value
Group D							
T0-T1	35.8±19.4	37	0	35 (100%)	0	-5.161	0.000
T0-T2	47.2±20.9	50	0	35 (100%)	0	-5.16	0.000
T0-T4	44.7±15.2	47	0	35 (100%)	0	-5.16	0.000
T0-T6	40.1±14.2	42	0	35 (100%)	0	-5.161	0.000
Group S							
T0-T1	13.9±9.2	14	0	33 (94.3%)	2 (5.7%)	-5.014	0.000
T0-T2	19.2±11.6	19	1 (2.9%)	34 (97.1%)	0	-5.08	0.000
T0-T4	24.2±12	25	0	34 (97.1%)	1 (2.9%)	-5.088	0.000
T0-T6	26±13.4	27	1 (2.9%)	34 (97.1%)	0	-5.144	0.000

Available evidence thus suggests that doses of dexamethasone administered prophylactically for postoperative nausea and vomiting (typically 4-8 mg) are unlikely to considerably increase intraoperative glucose concentrations. Although there was an increase in the blood glucose levels in patients administered dexamethasone, the increase was in a clinically acceptable range.

Our findings support the safety of dexamethasone in the perioperative setting. However, clinicians should use their judgment to monitor peri-operative blood glucose levels, even in non-diabetics administered with low-dose dexamethasone. It can be safely used routinely in patients undergoing laparoscopic cholecystectomy in view of the array of beneficial effects. In conclusion, denying steroid prophylaxis for postoperative nausea and vomiting for fear of a hyperglycemic response should be reconsidered given the limited effect of steroids on intraoperative blood glucose levels.

We limited our blood glucose measurements to 6 hours post administration of the test drug to avoid prolonged NPO hours, encourage early enteral feeds and minimize patient interruption to test blood glucose multiple times. Only non-diabetic patients were included in our study. The diabetic patients were treated with insulin for hyperglycemia. Hence, the results cannot be extrapolated to the diabetic population. Our study was not adequately powered to detect differences in the secondary outcome variables like nausea, vomiting, pain scores, or use of pain medications.

CONCLUSION

The administration of a single dose of 8 mg intravenous dexamethasone at the time of induction of general anaesthesia in non-diabetic patients undergoing laparoscopic cholecystectomy increases the blood glucose levels at different point intervals in the peri-operative period.

This increase was in a clinically acceptable range and was not severe enough to cause clinically apparent adverse effects.

Single dose of dexamethasone can be safely used for its beneficial effects and does not significantly increase the blood glucose levels in non-diabetic patients.

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