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ORIGINAL RESEARCH

Effect of Single Low-Dose Dexamethasone on Peri-operative Blood Glucose Levels

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Abstract

Background: Post-operative nausea and vomiting (PONV) is the second most common complaint reported after surgery with an incidence of 30%-80%. PONV is associated with numerous morbidities, hence prevention is beneficial. Dexamethasone is used as a prophylactic anti-emetic agent, however, being a corticosteroid, it could cause hyperglycaemia which is associated with a number of other adverse effects.
Objectives: To study the effect of a single low-dose intravenous dexamethasone given as a prophylactic anti-emetic agent on perioperative blood glucose levels.
Methods: Eighty-eight women who had elective myomectomy or hysterectomy under combined spinal-epidural (CSE) anaesthesia were randomised into two groups of 44 each. Following baseline blood glucose estimation, one group had 4 mg (1 ml) of intravenous dexamethasone 1-2 seconds after blood glucose check while the control group had 1 ml of normal saline. Blood glucose was measured every hour intra-operatively and two-hourly post-operatively till 12 hours after drug administration. Nausea, vomiting, dyspepsia, pain, motor block duration and urinary output were assessed hourly.
Results: The mean maximum change in blood glucose from baseline in the dexamethasone group was statistically significantly higher than in the control group, 51.00±26.57 mg/dl vs. 35.80±25.71 mg/dl ($p = 0.007$) so also was the mean maximum blood glucose, 153.93±31.63 mg/dl vs. 139.52±28.95 mg/dl ($p = 0.028$) respectively.
Conclusion: Intravenous dexamethasone at a single, low-dose (4 mg) used as a prophylaxis for nausea and vomiting is associated with significant increase in blood glucose concentration.

Keywords: Blood Glucose, Combined Spinal-Epidural Anaesthesia, Dexamethasone, Post-operative Nausea and Vomiting.

Introduction

Post-operative nausea and vomiting (PONV) is the second most common complaint reported (pain being the most common) after surgery [1] and has a general incidence of 30%. [2] Patients with no risk factor have 10% risk of having PONV. [2] In a subset of high-risk patients (patients with two or more risk factors for PONV), the incidence is as high as 80%. [2] PONV is associated with morbidities which include reduced patients' satisfaction, prolonged hospital stay, increased hospital expenses and in extreme cases, fluid and electrolyte imbalances. [2] Thus, the concept of prophylactic peri-operative anti-emetics. Gynaecological procedures and female gender are risk factors for PONV. [2] Female patients undergoing gynaecological surgeries are a subset of high-risk patients for PONV and this justifies the need for prophylactic anti-emetics for them.

Dexamethasone is a synthetic glucocorticoid [3] that has been found to reduce pain score and the need for analgesia. [4] It also has good anti-inflammatory, immunomodulating,[5] and antiemetic effects. [6] Dexamethasone is readily available and affordable; hence it is usually one of the first line anti-emetics.[7]
A single prophylactic dose of dexamethasone has been found to have significant anti-emetic effects.[6] Dexamethasone at a dose of 4 mg is as effective as ondansetron and droperidol as a sole antiemetic agent. [8] Intravenous 4 mg dexamethasone was found to have similar clinical effect as 8-10 mg dexamethasone in the reduction of PONV either as a single agent or when used in a combination therapy and it caused less hyperglycaemia when compared to the 8-10 mg dose.[9]

Hyperglycaemia is a documented complication from chronic steroid usage [10] but its occurrence after a single low-dose steroid still remains equivocal. [11,12] Hyperglycaemia may produce a number of adverse physiologic effects which includes osmotic diuresis and hypovolaemia, increased circulating inflammatory cytokine concentrations and adhesion molecule expression, decreased immune function, endothelial dysfunction, and electrolyte and acid-base imbalance. [13] The blood glucose concentration at which these effects are observed has not been identified, hence avoidance of peri-operative hyperglycaemia should be the goal. This randomized clinical study evaluated the effect of peri-operative dexamethasone therapy on the blood glucose levels of women who had similar anaesthetic and gynaecological surgeries.

Methods

This was a prospective, randomised, controlled, double-blinded clinical trial of the effect of a single dose 4 mg intravenous dexamethasone as a prophylactic anti-emetic on intra-operative and early post-operative blood glucose concentration of patients scheduled for elective gynaecological surgeries (myomectomy or hysterectomy) under combined spinal-epidural (CSE) anaesthesia. Patients between the ages of 18 and 65 years scheduled for elective myomectomy or hysterectomy, with American Society of Anesthesiologists (ASA) I or II physical status classification, Body Mass Index (BMI) between 18.5kg/m^2 and 30kg/m^2, height between 150cm and 180cm were included in the study. Patients who were known diabetics, with fasting blood glucose greater than 126mg/l (7mmol/l), HBA1c level greater than 6.5 %, 3 pluses of glucose on dipstick urinalysis, allergy to dexamethasone and other steroids, on long term steroids and those whose surgical procedure lasted less than 1 hour or longer than 4 hours, were excluded.
The sample size was calculated using the formula:

Minimum sample size (n) = $[2SD^2 (Z_{\alpha/2} + Z_{\beta})^2] / d^2$ [14]

Where SD = Standard deviation of the mean, Z = the critical value at 0.05 and d = effect size (difference between mean values).

The alpha error, α, was set as 0.05 and beta error, β, was set as 0.10 at a 90% power.

From a similar study by Abdelmalak [15] the effect size would be 28mg/dl.

Hence there were 40 patients in each arm of the study with extra 10% of the sample size for possible attrition bringing the final sample size to 88 with 44 patients in each study group. Ethical approval was obtained from Institutional Health Research Ethics Committee and written informed consent was obtained from the patients after explaining the procedure to them in detail.

A computer-generated block randomization allocation sequence was used which divided the 88 patients into two equal groups of 44 each: the test group and the control group. The allocations were put in sealed opaque envelopes. The envelopes were numbered sequentially from 1 to 88. The test group received 4mg (1ml) dexamethasone while the control received 1ml of normal saline at induction of anaesthesia while the researcher was blinded to the content administered. The serially numbered opaque envelope and the allocation cards in them were kept for later decoding after the study.

Routine pre-operative anaesthetic assessment was done a day before the surgery. Intravenous 10 mg metoclopramide was administered 45 minutes prior to surgery as a prophylactic antiemetic to all patients. In the theatre, pre-anaesthesia safety check was done. Baseline and continued monitoring of the vital signs which included oxygen saturation, respiratory rate, pulse rate, non-invasive blood pressure, electrocardiogram and peripheral temperature was done. A pre-neuroaxial block blood glucose concentration estimation was done using two millilitres of venous blood drawn into a fluoride oxalate test bottle, part of which was taken to the laboratory and a part evaluated using a glucometer for quality control purposes. The Mean Absolute Relative Difference (MARD) between the laboratory and glucometer blood glucose values were within 10%.

The patients were preloaded with 15mls/kg of normal saline and while in the sitting position, routine scrubbing of the back with antiseptic solution and draping was done. Using Tuffier's line as a landmark, L2-L3 intervertebral space was located and using size Fr18G Touhy needle and loss of resistance technique, the epidural space was located and an epidural catheter was inserted and secured. Afterwards, L3-L4 intervertebral space was located and using 25G pencil-point spinal needle, the subarachnoid space was located with free-flowing cerebrospinal fluid and subarachnoid block was instituted with 4 mls of 0.5% hyperbaric bupivacaine. The patients were placed supine to achieve a spinal block level of T5 dermatome which was assessed by loss of sensation to cold using a methylated spirit-soaked swab. The vital signs of the patients were checked every two minutes for the first 20 minutes or until stable and every five minutes, thereafter till the end of the surgery. The epidural component of the CSE block was activated 60 minutes after institution of the subarachnoid block with 20 mls of 0.5% isobaric bupivacaine injected at the rate of five millilitres every five minutes.

Post-neuroaxial block baseline blood glucose concentration was measured and recorded for the patients immediately after instituting the subarachnoid component of the CSE block. The study drugs (dexamethasone or normal saline) were then administered intravenously and the time of administration was recorded. Intra-operative fluid therapy was done with normal saline to compensate for deficit, maintenance and on-going losses. Glucose-containing intravenous fluids were avoided throughout surgery and the

period of blood glucose estimation post-operatively.

Blood glucose concentration was checked every hour after administration of the study drug and throughout the period of surgery and every two hours post-operatively until 12 hours after. The blood sample for glucose estimation was collected as capillary blood samples through finger prick from a warmed up upper limb to prevent erroneous blood glucose estimation from vasoconstricted cold extremities. The upper limbs were kept warm by covering them with blanket. The thumb used for pricks was anaesthetised using topical anaesthetic cream applied 30 minutes prior to surgery and was re-applied every two hours till the end of blood glucose estimation period to prevent pain from fingertip lancing. Total urinary output throughout surgery and timing of blood glucose estimation were measured and recorded.

Post-operative analgesia was by intermittent epidural top up of ten millilitres of 0.125% isobaric bupivacaine via epidural catheter. The first dose of the post-operative epidural analgesia top-up was given five hours after the intra-operative epidural anaesthetic dose and thereafter, every four hours till the end of the glucose estimation period. Post-operative fluid regimen was 500mls of normal saline four-hourly till the end of the glucose estimation period. Patients were evaluated for nausea, vomiting, dyspepsia, and pain every hour post-operatively till the end of blood glucose estimation period using the four-point ordinal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Break-through moderate to severe pain was treated with IV pethidine 50 mg. Episodes of moderate to severe postoperative nausea and vomiting were treated with IV ondansetron 4 mg while episodes of moderate to severe dyspepsia were treated with IV Omeprazole 40 mg and IV paracetamol infusion 1g. Patients with episodes of significant hyperglycaemia (random blood glucose greater than 200 mg/dl at any time) were managed by monitoring the blood glucose every 30 minutes for another one hour. If blood glucose persistently remained above 200 mg/dl, subcutaneous 10IU soluble insulin was administered every two hours until blood glucose was below 200 mg/dl. Bromage score of the residual motor block was assessed at the end of surgery and subsequently every hour till full power was regained (Bromage score 4).

The primary outcome measure was hourly blood glucose concentration and blood glucose concentration change from preoperative baseline in mg/dl while the secondary outcome measures were incidence and severity of post-operative nausea and vomiting assessed on a four-point ordinal scale, incidence and severity of immediate side effects associated with steroids (such as dyspepsia) assessed on a four-point ordinal scale, augmentation of effects of analgesics on pain assessed on a four-point ordinal scale, prolongation of motor block assessed with Bromage score and osmotic diuresis assessed with total urinary output.

The data was analysed using Statistical Package for Social science (SPSS) ® for Windows ® version 25 (SPSS Chicago IL, USA). Continuous variables were expressed as mean (±SD) and compared using the Student's t-test while categorical variables were compared using the Chi-Square test. A p-value less than 0.05 was considered significant.

Results

The comparison of the patients' clinical characteristics as shown in Table I show no significant difference. The type of surgery performed, amount of intravenous fluid administered, blood transfused and estimated intra-operative blood loss are described in Table II.

There was a general increase in the blood glucose concentration from baseline in both the dexamethasone group and the control group. However, there was a larger increase in the blood glucose level in the dexamethasone group than in the control group. There was no statistically significant difference in the baseline blood glucose of both groups before the administration of study drugs (p = 0.793).

Table I: Clinical characteristics of the subjects in both groups

Variable	*Dexamethasone n = 44*	*Control n = 44*	*Statistics*	*p-value*
Mean Age ± SD (years)	48.64±11.11	45.25 ± 9.37	t =1.54	0.120
ASA classification			$X^2 = 4.20$	0.120
ASA I	6 (13.6%)	7 (15.9%)		
ASA II	34 (86.4%)	37 (84.1%)		
Mean height ± SD (m)	1.61±0.05	1.63±0.05	-1.44	0.150
Mean weight ± SD (kg)	65.38±9.91	67.43±13.49	-0.81	0.420
Mean BMI ± SD (kg/m²)	25.00±3.23	25.23±4.15	-0.28	0.780

Table II: Surgical and medical characteristics in both groups

Variable	*Dexamethasone n = 44*	*Control n = 44*	*Statistics*	*p-value*
Type of surgery done			$X^2 = 1.73$	0.189
Myomectomy	14 (31.8%)	20 (45.5%)		
Hysterectomy	30 (68.2%)	24 (54.5%)		
Mean duration of surgery(mins)	131.95±45.64	119±23.14	t = 1.61	0.110
Mean Intra-op normal saline (mls)	2522.05±429.53	2661.82±639.53	t = 1.20	0.230
Mean estimated blood loss (mls)	593.18±359.35	500.00±307.45	t = 1.31	0.200
Blood transfusion			$X^2 = 3.67$	0.056
Yes	16 (36.4%)	8 (18.2%)		
No	28 (63.6%)	36 (81.8%)		
Mean blood volume transfused (mls)	687.50±250.00	750.00 ±267.26	t = -0.565	0.578

The mean baseline blood glucose for the dexamethasone group was 102.86±18.30 mg/dl compared to 103.73 ± 11.80 mg/dl in the control group. There was statistically significant difference in the mean maximum change in blood glucose from baseline for the dexamethasone group compared to the control group (p = 0.007) as shown in Table III.

Figure 1 shows the trend in the mean change in blood glucose from the baseline per hour. The increase in blood glucose from the baseline in the dexamethasone group compared to the control group was statistically significantly higher at 1 hour, 2 hours, 4 hours, 6 hours, 8 hours and 10 hours post-administration of the study drug with p values of 0.015, 0.044, 0.003, 0.000, 0.003 and 0.001 respectively. There was no statistically

significant difference in the change in blood glucose from baseline in both groups at 3 hours, 5 hours, 7 hours, 9 hours, 11 hours and 12 hours post-administration of the study drugs with p values of 0.654, 0.675, 0.052, 0.117, 0.814 and 0.116 respectively.

Table III: Occurrence of immediate side-effects of dexamethasone

Variable	*Dexamethasone n = 44*	*Control n = 44*	*Statistics*	*p-value*
Maximum blood glucose change (mean ± SD)	51±26.57	35.80±25.71	t = 2.74	0.007
Post-operative dyspepsia frequency	0 (0.00%)	2 (4.5%)		
Post-operative dyspepsia score (mean ± SD)	0.00±0.00	0.5±2.32	t = -1.43	0.156
Total urine output (mls) (mean ± SD)	1508.30±660.19	1576.48±671.27	t = -0.48	0.632
Post-operative pain score	4.89±3.66	6.30±4.47	t = -1.62	0.109
Post-operative pethidine consumption (mg)(mean ± SD)	23.86±29.51	23.86±33.22	t = 0.00	1.000
Time to full motor recovery (hours) (mean ± SD)	8.02±1.7	7.32±1.87	t = 1.83	0.071

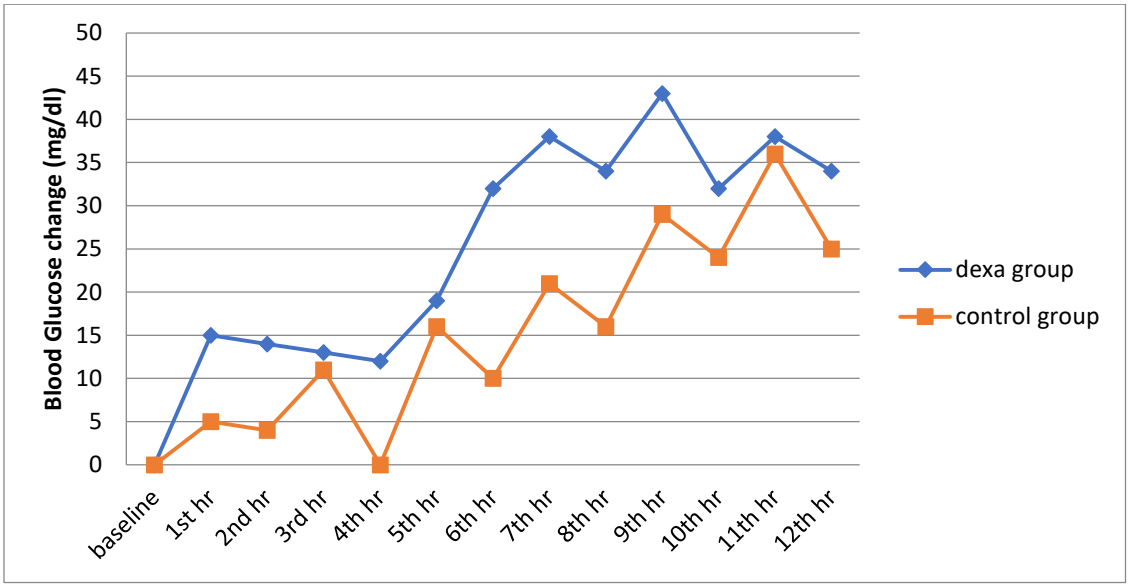

Figure 1: Mean hourly blood glucose change from the baseline
["dexa" - Dexamethasone"]

Figure 2 shows the trend in the hourly mean blood glucose. The difference in the mean blood glucose of both groups was statistically significant at 6 hours, 8 hours and 10 hours post study drug administration. The highest hourly mean blood glucose in the dexamethasone group was recorded at 9 hours post study drug administration with a value of 141.68±35.20 mg/dl. The highest mean blood glucose in the control group was recorded at 11 hours post administration of the study drug with a value of 135.94±35.28 mg/dl.

The maximum, median and minimum blood glucose levels recorded per hour for both groups are as shown in Table IV.

Throughout the study period, three blood glucose values greater than 200mg/dl (significant hyperglycaemia) were recorded in two patients in the dexamethasone group. One of these values (275mg/dl) was recorded one hour after the administration of the study drug while the remaining two values (228mg/dl and 221mg/dl) were recorded 9 hours after the administration of the study drug. None of the blood glucose values in the control group was greater than 200mg/dl at any point in time. The highest blood glucose value recorded in the control group was 190mg/dl and it was recorded 12 hours after administration of the study drug. There was no statistically significant difference in the hyperglycaemic episodes between both groups (p = 0.153). The mean maximum blood glucose values recorded in the dexamethasone group was 153.93±31.63mg/dl while that in the control group was 139.52±28.95 mg/dl. There was a statistically significant difference between these two blood glucose values (p = 0.028). The incidence of post-operative nausea and vomiting (PONV) is illustrated in Table V.

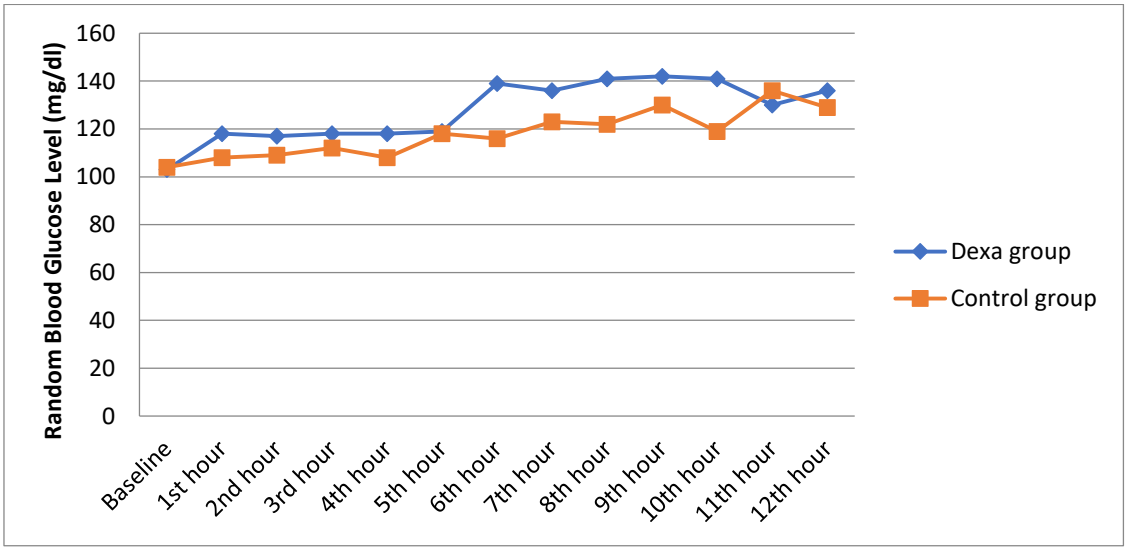

Figure 2: Mean hourly blood glucose levels
["Dexa" - Dexamethasone"]

Table IV: Maximum, median and minimum hourly blood glucose levels

Time from study drug administration (hours)	Maximum RBG (mg/dl)		Median RBG (mg/dl)		Minimum RBG (mg/dl)	
	Dexa	Control	Dexa	Control	Dexa	Control
1 hr	275	153	118.5	104.5	60	86
2 hrs	183	177	115.5	106.5	61	77
3 hrs	189	170	121.0	113.0	79	76
4 hrs	150	135	123.0	105.0	88	82
5 hrs	137	150	127.5	127.0	87	78
6 hrs	184	142	142.0	111.0	94	79
7 hrs	194	153	134.5	122.0	94	68
8 hrs	190	152	143.0	120.0	108	86
9 hrs	228	171	131.0	130.0	99	68
10 hrs	173	155	140.0	118.0	100	71
11 hrs	171	184	115.0	112.0	100	101
12 hrs	186	190	129.0	117.5	103	81

Dexa – Dexamethasone; RBG – Random Blood Glucose

Discussion

This randomised, double-blinded clinical study evaluated the effect of a low-dose intravenous dexamethasone given as prophylactic anti-emetic on the peri-operative blood glucose. The study showed that, a single dose of intravenous 4 mg dexamethasone given at the induction of anaesthesia caused significant increase in the intra-operative and post-operative blood glucose levels. The mean maximum change in blood glucose levels was 51.02 ± 26.57 mg/dl and 35.80 ± 25.71 in the dexamethasone and control groups respectively.

Table V: Occurrence of post-operative nausea and vomiting

Variable	Dexamethasone n = 44	Control n = 44	Statistics	p-value
Post-operative nausea incidence	6 (13.6%)	7 (15.9%)		
Mean Post-operative nausea score	0.34±1.1	0.48±1.37	t = -0.52	0.608
Post-operative vomiting incidence	2 (4.5%)	5 (11.4%)		
Mean Post-operative vomiting score	0.14±0.63	0.23±0.64	t = -0.67	0.505

Chalifoux and colleagues [16] in their study, found a significant increase in the blood glucose concentration from baseline when 4 mg intravenous dexamethasone (given) was compared to placebo in test subjects, which was similar to the finding in the present study. The mean change in blood glucose concentration in the placebo group of their study was much lower than the placebo group in the present study. This may be partly due to the duration of the surgery which was less than 1 hour in their study but no surgery was less than 1 hour in the present study. Therefore, the hyperglycaemic response to the stress of surgery could have been limited in their study population.

Similarly, Peter *et al.* [17] found significantly raised blood glucose levels following the administration of a single intravenous dose of dexamethasone to non-diabetic patients for middle ear surgery when compared to placebo. The mean blood glucose level in the dexamethasone group was higher than the level in the non-dexamethasone group. Even though, the surgical intervention may not be similar, the glycaemic effect of dexamethasone was still same and evident.

The incidence of post-operative nausea in the present study was lower (13.6%) in the dexamethasone group compared to 15.9% in the control group, though this difference was not statistically significant. A similar finding was reported by Khatiwada *et al.* [18] with 40% in the dexamethasone group and 67.5% in the control group. There was also a lower incidence of post-operative vomiting in the dexamethasone group, 4.5% compared to 11.4% in the control group. Notwithstanding that all the patients in the present study had metochlopramide, the antiemetic effect of dexamethasone further reduced the incidence of post-operative nausea and vomiting in the subjects that received it. A similar effect was also recorded by Olajumoke *et al.* [6] in their study. Post-operative pain-scores in the dexamethasone group in the present study was lower than in the control group but this difference was not statistically significant. The average post-operative pethidine (opioids) consumption was the comparable for both groups. This finding was similar to the study of Mehdirratta *et al.* [19] in which there was no significant difference in the cumulative opioids

consumption and pain scores in patients who had caesarean section under subarachnoid block that received dexamethasone and those who did not receive it.

Conversely, Waldron *et al.* [20] found 13% reduction in the opioid consumption in the first two hours post-operatively in the patients that received dexamethasone and a 10.3% reduction at 24 hours post-operatively. This difference might be explained by the use of epidural analgesia as the main form of analgesia in this study, which might have reduced the need for opioid in both study groups making the difference in the need for opioids, not significant between the two groups.

Sourabh *et al.* [21] did not demonstrate a significant difference in the duration of motor blockade after sub-arachnoid block between the dexamethasone and placebo group. Similarly, Shalu *et al.* [22] could not demonstrate a significant difference in the duration of motor blockade between the dexamethasone group and the placebo group in the study. Though the duration of motor blockade was longer, 169.5 minutes, in the dexamethasone group compared to 163.17 minutes in the control group. These were similar to what was found in the present study where there was no significant difference in the duration of blockade between the dexamethasone and control groups. Nevertheless, the mean duration of motor blockade following CSE was longer in the dexamethasone group compared to the control group.

There was no epigastric pain from the use of dexamethasone whereas 4.5% in the placebo group had epigastric pain in the present study. The two patients in the placebo group that had epigastric pain during the monitoring period in the present study were known peptic ulcer disease patients.

The urinary output during the period of the study was used as a surrogate measure of osmotic diuresis from hyperglycaemia on the premise that hyperglycaemia causes osmotic diuresis, by increasing urinary output. Total urinary output in the dexamethasone group and the control group were comparable despite the blood glucose level in the dexamethasone group being considerably higher than in the control group. Hence, dexamethasone may not cause hyperglycaemia that would lead to osmotic diuresis. The effects of dexamethasone on blood glucose after 12 hours could not be assessed in the present study as the patients had been commenced on glucose-containing fluids.

Conclusion

In patients scheduled for myomectomy or hysterectomy, single low-dose intravenous dexamethasone given for prophylaxis for post-operative nausea and vomiting, raised blood glucose concentration significantly but also caused substantial hyperglycaemia in very few patients. Prophylactic dexamethasone administration did not significantly reduce the incidence of post-operative nausea or vomiting, prolong motor blockade, reduce post-operative pain scores, predispose to osmotic diuresis nor cause dyspepsia in the subjects.

Authors' Contributions: DSA, FOM, OBB conceived the study. DSA designed the study and did the literature review. DSA, OOO, OAA and ABO did data analysis and interpretation. All the authors drafted the manuscript and revised it for sound intellectual content and approved the final version.
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