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A Randomised Controlled Study Evaluating the Efficacy of Dexamethasone in Preventing Post-operative Nausea and Vomiting and its Effect on Blood Glucose

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Abstract

Context: Persistent vomiting leads to poor patient satisfaction, delayed wound healing, dehydration and electrolyte disturbances. In addition, vomiting or retching can sometimes result in more serious complications like aspiration, wound dehiscence, increased intracranial pressure, oesophageal rupture and pneumothorax. The expanding number of procedures performed as daycare surgeries has led to the increasing use of dexamethasone for PONV. *Aims:* The present study is to evaluate the optimum dose of dexamethasone for prevention of PONV and to measure the extent of the hyperglycemic side effects post-operatively in non-diabetics. *Settings and Design:* Prospective randomized controlled comparative study. *Methods and Materials:* After approval from the Institutional Ethics Committee, study was conducted on 135 patients of the American Society of Anesthesiologists (ASA) Grade I, II and III, aged between 20 to 60 years and included both genders that underwent elective surgeries under general anesthesia. Patients were randomized into 3 Groups to assess the efficacy of different doses of dexamethasone for prevention of PONV. All post-operative cases were followed up at 0, 12 and 24 *hours*, PONV and blood sugar levels were measured. PONV was being evaluated on a five-point ordinal scale. *Statistical analysis used:* Percentage analysis was used for categorical variables and the mean and SD was used for continuous variables. ANOVA with Tukey's Post-hoc test was used for the significant difference and for the repeated measures of ANOVA was used with Bonferroni correction to control the Type I error on multiple comparisons. The collected data were analysed with IBM® SPSS statistics software 23.0 Version. *Results:* Among categorical variables, p values for age (*p* - 0.611), gender (*p* - 0.533), ASA status (*p* - 0.234) with Chi-square testing were not significant. It is interesting to note that only 1 (2.2%) patient had nausea and vomiting in Group C compared to 5 (11.1%) in Group A and 3 (6.7%) in Group B in the immediate post-operative period. Post-operative blood glucose levels varied significantly in different Groups. In Group A blood sugar levels were 106.93 ± 14.426 *mg/dl*, Group B 117.31 ± 11.791 *mg/dl* and Group C 129.49 ± 16.170 *mg/dl* respectively in the immediate post-operative period. *Conclusions:* The benefits of administering higher doses of IV Dexamethasone should be weighed against the potential side-effects of short-lasting hyperglycemia.

Keywords: Dexamethasone; PONV; Blood glucose; Antiemetics.

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Introduction

With the introduction of general anesthesia in the first half of the nineteenth century, managing post-operative nausea and vomiting (PONV) has always been a challenge. In 1848, John Snow recognized and pioneered the management, eighteen months after the introduction of chloroform to anesthesia. The term PONV is typically used to describe nausea and/or vomiting or retching in the post-anesthesia recovery room or in the first *24 hours*. There are patient, anesthesia and surgery-related risk factors that increase the incidence of post-operative nausea and vomiting, which invariably results in increased morbidity and poor patient outcome. They often rate PONV as worse than post-operative pain.[1]PONV usually resolves or is treated without a sequel, but may require unanticipated hospital admission and delayed discharge from recovery room or the hospital.[2]

Persistent vomiting leads to poor patient satisfaction, delayed wound healing, dehydration and electrolyte disturbances. In addition, vomiting or retching can sometimes result in more serious complications like aspiration, wound dehiscence, increased intracranial pressure, oesophageal rupture and pneumothorax. Despite the availability of a number of anti-emetic drugs, no single agent is 100% effective against PONV. This may be because PONV is multifocal in origin and stimulus. In recent years, interest has been focused on the combination of drugs. Ondansetron and dexamethasone are being used successfully to treat emesis refractory to ondansetron alone.[3] Hence, the present study was carried out to find the role and safety of ondansetron plus dexamethasone in preventing PONV in patients undergoing elective surgical procedures under general anesthesia and its effect on blood sugar. Non-diabetic surgical patients, especially those suffering from acute illnesses, often become hyperglycemic. Physiological stress associated with trauma, serious illness and surgery, can cause insulin resistance, glucose intolerance, and hyperglycemia, a syndrome often referred to as diabetes of injury.[4] Whether peri-operative hyperglycemia causes serious complications to remain controversial, but high plasma glucose concentrations are inflammatory and decrease immune competence. Peri-operative use of steroids like dexamethasone is often administered because of its effective antiemetic action. Some clinicians have used steroids to reduce post-operative edema, inflammation and fatigue. The most important complication of peri-operative steroid administration is immune suppression and so impaired resistance to infection, besides that steroids also cause insulin resistance and hyperglycemia. Dexamethasone is a synthetic adrenocortical steroid and many of procedures performed as daycare a surgery has led to the increasing use of dexamethasone for PONV. It is regarded by many as an ideal peri-operative agent which is cheap, readily available for the prevention of PONV. It also promotes appetite, a feeling of well-being which is associated with earlier discharge from daycare surgery units. Hence, it is used widely now-a-day. Side-effects are generally thought to be linked to long-term steroid use.

So, the present study is to evaluate the optimum dose of dexamethasone for prevention of PONV and to measure the extent of the hyperglycemic side effects post-operatively in non-diabetics.

Materials and Methods

After approval from the Institutional Ethics Committee a prospective randomized controlled comparative study was conducted for *4 months* from *March 2018* to *June 2018* on 135 patients of the American Society of Anesthesiologists (ASA) Grade I, II and III, aged between *20* to *60 years* and included both genders that under went elective surgeries under general anesthesia. Patients with the physical status of ASA IV, patients who received opioids or anti-emetic agents *48 hrs* prior to surgery and patients receiving Total Intravenous Anesthesia (TIVA) or target-controlled infusion (TCI) intra-operatively were excluded from the study. The study conformed to the Helsinki Declaration (World Medical Association, 1995). Written informed consent from each patient was taken before enrolment in the study. Patients were randomized into 3 Groups as under:

Group A ($n = 45$) –Non-diabetic Patients receiving ondansetron *4 mg* only;

Group B ($n = 45$) –Non-diabetic Patients receiving ondansetron *4 mg* and dexamethasone *4mg*;

Group C ($n = 45$) –Non-diabetic Patients receiving ondansetron *4 mg* and dexamethasone *8 mg*.

Sample size calculation: The number of participants required in each group was 43.8 for a confidence level of 95% and power of 80%. However, for the sake of greater accuracy, it is decided to include 45 cases in each Group.

$$\text{The sample size (n)} = \frac{2 \times \{z\,(1-\alpha/2)+z\,(1-\beta)\}}{\Delta^2}$$

$Z_{(1-\alpha/2)}$ is the alpha error whose value for a significance level of 5% (confidence level of 95%),

is 1.96 and $z_{(1-\beta)}$ is the beta error or the power of the study whose value power of 80% is 0.8416 and

$$\Delta^2 = (p_1-p_2)^2 \quad \text{where } p' = p_1 + p_2$$
$$p'(1-p')^2$$

$p_1 = 0.35$ and $p_2 = 0.1$ $p' = (0.35 + 0.1)/2 = 0.225$

$\Delta^2 = (0.35-0.1)^2/0.225\ (1-0.225) \times = 0.0625/0.225 \times 0.775 = 0.0625/0.1744 = 0.358$

Alpha error at 5% significance level = 1.96

Beta error (power) at 80% = 0.8416

Sample size (n) = $2\ (1.96 + 0.8416)^2/0.358 = 15.698/0.358 = 43.8$ rounded off to 45 for easy calculation.

Total sample size for the three Groups = 3 × 45 = 135

The sample size for this study is 135 (3 × 45) cases. The required sample size was 135 cases for a significance level of 5% (confidence level of 95%) and a power of 80%. Based on a previous study[16] which assessed efficacy of different doses of dexamethasone for prevention of PONV, the authors had reported the figures for incidence of PONV in the ondansetron the only group as 28 out of 80 ('p^1' = 28/80 = 0.35) and the ondansetron and dexamethasone group as 8 out of 80 ('p^2' = 8/80 = 0.1) respectively.

All the patients who were scheduled to undergo elective surgeries and who satisfied the inclusion criteria and exclusion criteria were included in the study.

Observer 1: Anesthesia resident performing the study, did the pre-operative evaluation, checked for the inclusion and exclusion criteria and obtained informed written consent. The same observer did the post-operative assessment of the patient.

Observer 2: Primary anesthesia consultant who is responsible for peri-operative management.

Routine Pre-anesthetic checkup was done prior to the surgery and routine investigations were done as per the protocol. After checking the identity and consent, the patients were shifted to the operation room, multipara monitor attached and anti-emetics were administered after induction of anesthesia. In the post-operative period, patients vitals were monitored. All post-operative cases were followed up at *0,12* and *24 hours*, PONV and blood sugar levels were measured.

PONV was being evaluated on a five point ordinal scale:

0 = none, 1 = Nausea, 2 = Retching, 3 = Vomiting, 4 = Severe Vomiting (> 4 episodes);

In patients who complained of vomiting-metoclopramide/ondansetron/prochloromethazine were used as rescue anti-emetics.

Statistical Analysis

The information collected regarding all the selected cases were recorded in a Microsoft Excel spreadsheet. The collected data were analysed with IBM® SPSS statistics software 23.0 Version. To describe the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean & SD was used for continuous variables. To find the significant difference in the multivariate analysis the one way ANOVA with Tukey's Post-Hoc test was used and for repeated measures, the repeated measures of ANOVA was used with Bonferroni correction to control the type I error on multiple comparisons. Chi-square test was used to find the significance in categorical data. In all the above statistical tools the probability value 0.05 was considered as significant level. $p < 0.05$ was considered to be significant.

Results

A total of 135 patients between age group *20–60 years*, 75 males (55.6%) and 60 females (44.4%), physical status ASA I–III underwent elective surgery under general anesthesia were included in the study. Table 1 summarizes the demographic and clinical characteristics of patients.

Table 1: Demographic characteristic of patients

	Group A	Group B	Group C	Total
Age				
20–30	12	12	5	29
31–40	12	12	13	37
41–50	13	13	17	43
51–60	8	8	10	26
Sex				
Female	18	19	23	60
Male	27	26	22	75
ASA				
I	29	21	20	70
II	14	23	24	61
III	2	1	1	4

p-value for age, sex and ASA are 0.611, 0.533 and 0.234 which were statistically insignificant, so our study was comparable with age, sex and ASA physical status. Table 2 shows the continuous variables like pulse rate, systolic and diastolic blood pressure and blood sugar level.

Table 2: Continuous variables

	0 hr	12th hr	24th hr
Pulse rate			
Group A	79.89	78.38	77.78
Group B	76.84	74.58	73.64
Group C	78.22	75.07	74.04
Systolic blood pressure			
Group A	127.40	123.29	121.78
Group B	128.60	122.44	124.00
Group C	132.44	126.44	124.22
Diastolic blood pressure			
Group A	82.20	81.11	80.89
Group B	81.58	80.22	80.44
Group C	79.24	81.56	78.67
Blood Sugar levels			
Group A	106.93	109.64	108.07
Group B	117.31	117.82	118.51
Group C	129.49	124.53	122.73

On comparison of blood sugar levels among 3 study groups, dexamethasone was associated with higher incidence of post-operative hyperglycemia in Group A and B whereas it was decreased in Group C. *p* value is 0.017 and 0.003 which is significant between groups.

During *24 hr* of follow-up, it was observed that in Group A, B and C post-operative nausea and vomiting at baseline (*0 hr*) was 11.1%, 6.7% and 2.2% respectively whereas it was absent during 12*th* and 24*th* hr as shown in (Fig. 1). So, the incidence of rescue anti-emetics in Group A, B and C was 11.1%, 6.7% and 2.2% respectively. *p* value was 0.240 which was not significant.

Discussion

Several important findings have emerged from the meta-analysis of the previous study[5] on the effect of dexamethasone for the prevention of post-operative nausea and/or vomiting. Different from Karanicolas *et al.*,[6] who detected dose effects of dexamethasone on the incidence of PONV. No single drug has proved to be a universal solution to PONV. It is not advisable to give the same drug in multiple doses because of saturation effects and safety, so, a combination of anti-emetic and corticosteroids are a possibility. Ondansetron has generally been considered as the most effective medication in preventing and managing PONV. In other view, Tramèr and Walder[7] reported more anti-vomiting than anti-nausea properties of ondansetron, other commonly used medication to prevent PONV. Nevertheless, it seems that previous comparisons between these individual

Pairwise Comparisons

(I) BSL		Mean Difference (I-J)	Std Error	Sig	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
A	B	4.956*	1.707	0.017	0.707	9.204
	C	6.756*	1.885	0.003	2.063	11.448
B	A	-4.956*	1.707	0.017	-9.204	-0.707
	C	1.800	0.951	0.195	-0.566	4.166
C	A	-6.756*	1.885	0.003	-11.448	-2.063
	B	-1.800	0.951	0.195	-4.166	0.566

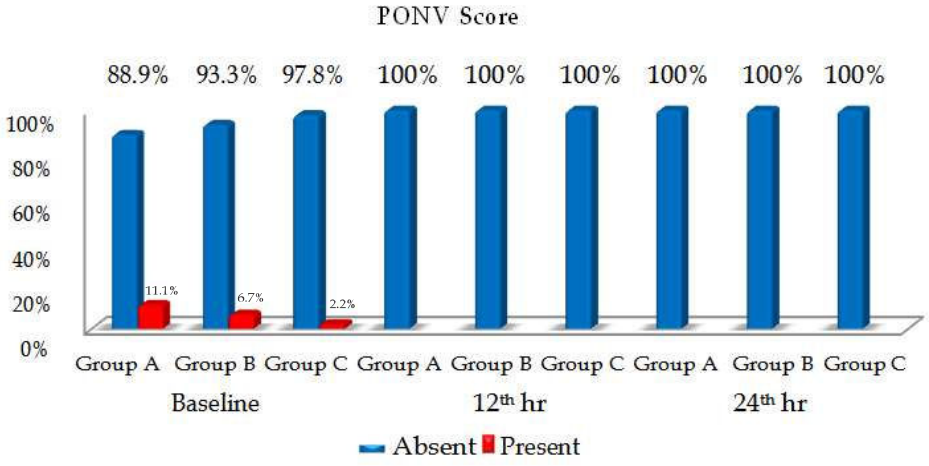

Fig. 1: PONV score among 3 Study Groups

drugs did not show a significant benefit in favor of a specific drug.[8]

We have conducted a study on 135 patients who underwent various elective surgeries under general anesthesia in the non-diabetic population. They were randomly distributed into three Groups of 45 each depending upon the anti-emetic agent given and data obtained were tabulated and analyzed statistically with reference to age, sex, ASA physical status, pulse rate, blood pressure, PONV score and blood sugar levels.

Among categorical variables, *p* values for age (*p*-0.611), gender (*p*-0.533), ASA status (*p*-0.234) with Chi-square testing were not significant, hence our patients were comparable with age, sex, -ASA status and equally distributed among the groups. It is interesting to note that only 1 (2.2%) patient had nausea and vomiting in Group C compared to 5 (11.1%) in Group A and 3 (6.7%) in Group B in the immediate post-operative period. However, rescue anti-emetic medication was given to those patients who had PONV. *p*-value is 0.240 in the immediate post-operative period which can be compared within the groups.

The current trend is focused on combination therapy because there is no single effective agent against PONV, because of its multifactorial in origin. The idea of combination therapy for prevention and treatment of PONV came from various studies where ondansetron and dexamethasone have been used successfully to treat emesis refractory to ondansetron alone but none of the studies has evaluated the optimum dose of dexamethasone required for prevention of PONV and measured the extent of the hyperglycemic side effects post-operatively. Hence, among the continuous variables, our interest was on post-operative blood sugars levels of all the groups.

Patient variables may affect the incidence of peri-operative hyperglycemia, which includes age, sex, body weight, and pre-operative medications.[9] Our study focussed on non-diabetics because it may be more harmful and unethical to use a high dose of dexamethasone in diabetic patients. So, we have evaluated and compared the effect of blood glucose levels and PONV with different doses of dexamethasone in these 3 Groups of patients. Morerises in blood glucose concentration in the dexamethasone group may be due to increase in gluconeogenesis[10] and development of insulin resistance induced by it which was seen as early as *4 hrs* after induction of anesthesia. Previous study[11] correlate with the study of Jeffrey *et al*.[12] who observed that a single dose of dexamethasone produceda significant increase in blood glucose concentration.

Post-operative blood glucose levels varied significantly in different groups. In Group A blood sugar levels were *106.93 ± 14.426 mg/dl*, Group B *117.31 ± 11.791 mg/dl* and Group C *129.49 ± 16.170 mg/dl* respectively in the immediate post-operative period. A *p*-value of 0.0005 was found when ANOVA and Tukey's Post-hoc test were used for blood sugar in *0 hours*.

Blood sugar levels were lower in patients with a lower dose of dexamethasone (*4 mg*) but PONV is marginally higher than in patients with a higher dose of dexamethasone (*8 mg*). Incidence of PONV is more in Group A compared to B and C in the initial post-operative period but *12 hours* and *24 hours* post-operatively there is no difference between the groups.

According to our study blood sugar levels were relatively higher in Group C patients than other two Groups even after *12* to *24 hours* post-operatively but the mean difference was relatively lesser than immediate post-operative period. However, the incidence of PONV is relatively less when compared to Group A.

Limitations of the study:

- The study had to be done within a fixed time frame;
- Some patients who were enrolled were excluded from analysis as there was a significant violation of the protocol;
- Delay in wound healing with the use of dexamethasone was not studied;
- We did not document the incidence of wound infection in the study groups;
- None of the patients in study groups developed life-threatening arrhythmia. However, we didn't do an ECG routinely to look for the above in the post-operative period;
- All types of elective surgeries under general anesthesia were compared rather than specific types of procedures;
- Some patients who were enrolled were discharged within *24 hrs* of the surgery which led to their exclusion.

On conclusion, as there are different receptor systems involved in the etiology of PONV, a combination of agents acting on different receptors

results in better prophylaxis of PONV, as no single agent is entirely effective in preventing it. Prophylactic administration of a combination of IV Ondansetron (*4 mg*) with IV Dexamethasone (*4 mg*) is safe and more effective compared to IV Ondansetron (*4 mg*) alone in reducing incidence of PONV in patients undergoing elective surgeries under general anesthesia. Although higher doses of IV Dexamethasone (*8 mg*) are frequently used for reducing the incidence of PONV, it results in maximum hyperglycemia in the immediate post-operative period. Thus, the benefits of administering higher doses of IV Dexamethasone should be weighed against the potential side-effects of short-lasting hyperglycemia. None of the patients in our study required correction for hyperglycemia, but it would be prudent to keep a close watch on blood sugar levels in the immediate post-operative period.

Based on our study, considering the risks and benefits, we recommend that IV ondansetron (*4 mg*) with IV dexamethasone (*4 mg*) as the ideal drug combination to effectively reduce PONV with minimal side effects.

Key Messages

Prophylactic administration of a combination of IV Ondansetron (4 *mg*) with IV Dexamethasone (4 *mg*) is safe and more effective compared to IV Ondansetron (4 *mg*) alone in reducing incidence of PONV.

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