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Study Of Haemodynamic and Endocrine Stress Responses Following Carbon Dioxide Pneumoperitonium

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ABSTRACT

Background: The aim of the study is to investigate the effect of oral gabapentin or clonidine versus placebo premedication on haemodynamic and endocrine responses in patients of American Society of Anesthesiology (ASA) physical status I and II undergoing laparoscopic cholecystectomy.

Methods: This was a randomized prospective double-blinded comparative study of 75 ASA I and II patients with three groups: clonidine, gabapentin and placebo group having 25 patients in each. They were randomly allocated to receive 600 mg oral gabapentin or clonidine 150 mcg one hour prior to induction of anesthesia and a placebo group. Hemodynamic parameters were recorded before pneumoperitonium (PP) and every 5 minutes till 35 minutes of post PP. Blood samples for serum glucose and cortisol were collected before PP and 10 mins after PP .The investigators were blinded to what the patients received.

Results: With similar demographic profiles and baseline haemodynamics in three groups ($p>0.05$) significant rise in haemodynamic parameters were observed in placebo group at different time points before and following PP where as those parameters remained stable in gabapentin and clonidine group ($p<0.05$). The serum cortisol level was high in placebo group before PP than in two other groups, $p<0.05$. The same marker measured at 10th minute after PP was significantly higher in placebo group than that in clonidine or gabapentin group, $p<0.05$.

Conclusions: Oral clonidine or gabapentin premedication offers intraoperative haemodynamic stability in laparoscopic cholecystectomy. When serum cortisol is taken as a stress marker, gabapentin group exhibited significant attenuation of stress of PP, $p <0.05$.

Keywords: clonidine, cortisol, gabapentin, haemodynamics, pneumoperitonium.

INTRODUCTION

Laparoscopic technique has become a treatment of choice due to its minimal invasiveness, less pain and early ambulation. Laparoscopic cholecystectomy demands creation of PP for visualization, their dissection and meticulous hemostasis. Carbon dioxide is the principal gas used for this purpose. Despite proved advantages over conventional open surgery, laparoscopic intervention is not without its challenges on cardiovascular, pulmonary and endocrine balance.[1-4] PP causes an increase in blood pressure, systemic and pulmonary vascular resistance.[5] The clinical significance of this change in healthy patients undergoing this procedure may be tolerable, but the impact might cause substantial harm to patients with preexisting cardiovascular comorbidities. Different pharmacological agents have been used as premedicants aiming to control the physiological changes that might occur during laparoscopic surgery.[5,6] This study was designed to evaluate the haemodynamic changes and endocrine response (serum glucose and cortisol changes) before and after PP in patients premedicated

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either with clonidine, gabapentin or placebo undergoing routine laparoscopic cholecystectomy.

METHODS

A randomized prospective double-blind comparative study was done in Kathmandu medical college teaching hospital from January 2010 to July 2010. Total of 75 ASA I and II patients aged 25- 60 years and weight of 40-70 kg work randomized during carbondioxide PP in laparoscopic cholecystectomy. Written informed consent was obtained from patients and the ethical clearance was taken from institutional ethics committee. Patients with history of uncontrolled hypertension, adrenal mass, diabetes mellitus, ischemic heart disease, bronchial asthma and corpulmonale, acute cholecystitis, pancreatitis were not included in the study. Patients with history of seizure disorder and previously taking gabapentin, phenytoin or drugs which may affect the serum cortisol level like clonidine, glucocorticoids, estrogen were also excluded from the study. All patients were premedicated with diazepam 5 mg and metoclopramide 10 mg orally night before surgery. Patients were randomly assigned into clonidine, gabapentin or placebo group. Patients in clonidine group were given 150 mcg of clonidine orally and gabapentin group received 600 mg of gabapentin one hour before surgery and the placebo group received 150 mg of oral ranitidine as a placebo. The investigators were blinded to what the patients received.

On arrival to operation theatre routine monitors electrocardiogram, non invasive blood pressure, pulse oxymetry were applied to the patients and the baseline haemodynamic parameters: Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood pressure (DBP), Mean arterial blood pressure (MAP) were recorded. Intravenous access was secured and Induction of general anaesthesia was carried out with intravenous propofol 2 mg/kg and fentanyl 2 mcg/kg. Muscle relaxation was achieved with intravenous rocuronium 1 mg/kg. Anaesthesia was maintained with oxygen 30% with air and halothane. Patients were kept in intermittent positive pressure ventilation and end-tidal carbon dioxide (ETCO2) was maintained at 35-40 mm of Hg adjusting tidal volume and rate of respiration.

PP was created by insufflation with carbon dioxide at a flow rate of 1 L/min and intraabdominal pressure was kept 12 mm of Hg during the surgery. The haemodynamics were recorded at different points of time before PP and post PP at 5, 10, 15, 20, 25, 30 and 35th minute. During the procedure the rise in mean arterial blood pressure more than 20% of the baseline was treated with increasing halothane concentration and or with injection labetalol.

Prior to PP blood samples for serum glucose and cortisol were taken in each patient. Next blood sample was then taken at 10 minutes post PP. The samples were preserved and sent to the laboratory as per instructions from biochemical laboratory. To avoid the possible diurnal variation in serum cortisol, cases were scheduled from 9 am to 1 pm. The pre PP and post PP blood glucose and serum cortisol within the group and amongst the groups were subjected for statistical analysis. Following conclusion of surgery residual neuromuscular block was reversed with intravenous neostigmine 0.5 mg/kg and atropine 0.02 mg/kg. After extubation patient was shifted to postoperative ward for futher needed care.

Glucose and cortisol values were presented as mean ± SD (standard deviation). Data were analysed by Student's *t*-test for unpaired observations. ANOVA test was applied to compare the changes in SBP, DBP and HR values. A probability of less than 0.05 was considered statistically significant. The statistical package SPSS (Statistical package for social sciences) 14.0 (SPSS® Inc., Chicago, IL, USA) was used.

RESULTS

Demographic profiles of the patients in three groups were not different in terms of age and body weight (Table 1). The inter group and within the group serum glucose pre and post PP was not significant statistically, p>0.05. The cortisol level in placebo group increased from 19 to 33 mcg/dL which was found to be significantly higher compared to both clonidine and gabapentin group. The cortisol value in gabapentin group decreased significantly from 15 mcg/dL pre pneumoperitonium value to 8 mcg/dL at 10 mins post pneumoperitonium, p=0.01 (Table 2). The clonidine group had reduced level of serum cortisol post PP than that in pre PP value, but statistically the difference was not significant, p=0.06.

Table 1. Demographic profile of patients in the study groups.

Group	Age (yr)	Weight (Kg)	Sex
Clonidine (n=23)	43.5 ± 12.2	62.5 ± 9.3	M=6,F=17
Gabapentin (n=24)	38.0 ± 11.0	62.8 ± 8.6	M=4,F=20
Placebo (n=24)	42.7 ± 14.7	55.7 ± 9.3	M=4,F=20
	p= 0.35	P= 0.30	

Base line heart rate (HR) and before PP Heart rate was not different in three groups p>0.05. Following PP till 35 minutes HR remained consistently increased than base line value in placebo group, whereas it was stable in both clonidine and gabapentin group. The change in HR was significant in patients belonging to placebo group when compared to clonidine or gabapentin group, p<0.05.

Table 2. Serum glucose and cortisol before and after pneumoperitonium.

Group	Serum Glucose(mg/dL) Before PP	Serum Glucose(mg/dL) After PP	p-value	Serum Cortisol(mcg/dL) Before PP	Serum Cortisol(mcg/dL) After PP	p-value
Clonidine	98.2 ± 16.2	97.7 ± 14.7	0.80	9.5 ± 3.7	11.6 ± 4.6	0.06
Gabapentin	96.6 ± 12.6	94.5 ± 12.4	0.16	14.7 ± 8.1	8.3 ± 5.7	0.01
Placebo Group	92.4 ± 16.3	92.7 ± 14.1	0.23	19.3 ± 8.4	33.3 ± 8.3	0.00
p-value	0.7	0.4		0.07	0.03	

The change in SBP within the group at different stages was statistically not significant. When compared to the base line values both in clonidine and gabapentin groups, p>0.05. The rise in SBP at different time points was found to be significant statistically in placebo group, p<0.05. The mean SBP values in placebo group were significantly higher in comparison to clonidine and gabapentin group, p<0.05.

The base line DBP values were similar in three groups. At different times as studied the DBP was not different significantly in both clonidine and gabapentin group when compared to respective baseline value, p>0.05. Within the placebo group the DBP was in increasing trend following PP and the rise was statistically significant, p<0.05. This rise in DBP in placebo group was statistically significant when compared to the values with clonidine or gabapentin group, p<0.05.

The baseline MAP and the MAP before pneumoperitonium were not different in three groups p=0.33. This value failed to hold stability through different time points post PP in placebo group when comparison was done within the group or with both clonidine or gabapentin group, p<0.05 (Table 2).

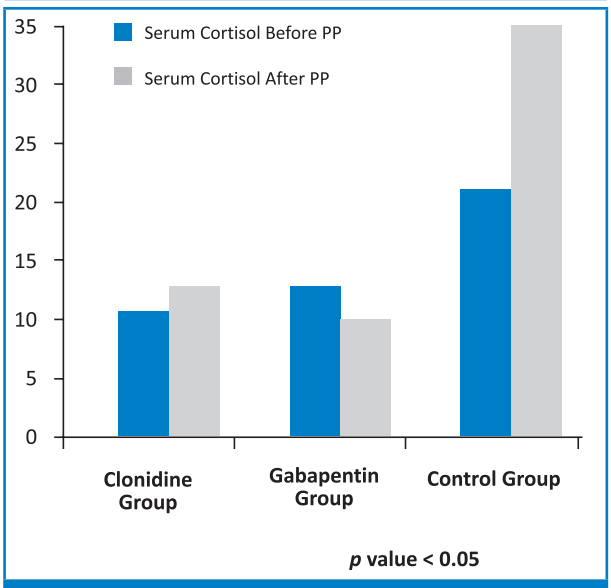

Figure 1. Serum cortisol level in three groups before and after pneumoperitonium.

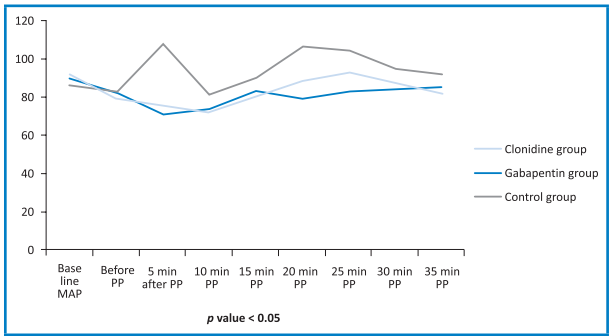

Figure 2. Mean arterial blood pressure (MAP) at different time interval.

Table 3. Mean arterial blood pressure (MAP) at different time interval

	Clonidine group	Gabapentin group	Placebo group	p-value
Base line MAP	91.4 ± 12.5	89.3 ± 81.4	86.5 ± 14.7	0.33
Before PP	79.1 ± 7.8	82.0 ± 3.0	111.7 ± 9.1	0.12
5 min after PP	75.1 ± 10.0	71.0 ± 9.1	107.6 ± 13.1	0.00
10 min PP	72.0 ± 9.3	74.0 ± 8.6	114.5 ± 6.9	0.03
15 min PP	79.4 ± 10.0	83.0 ± 15.0	115.0 ± 3.1	0.10
20 min PP	88.3 ± 7.0	79.0 ± 5.1	109.0 ± 8.0	0.03
25 min PP	92.6 ± 4.0	82.6 ± 14.0	104.3 ± 9.1	0.00
30 min PP	87.6 ± 2.8	84.0 ± 11.0	95.0 ± 10.3	0.00
35 min PP	82.1 ± 5.6	85.0 ± 10.8	92.0 ± 10.3	0.09

DISCUSSION

This study shows that carbon dioxide PP with intraabdominal pressure of 12 mm of Hg causes significant haemodynamic alteration and rise in serum cortisol in ASA I and II patients when no stress attenuating anaesthetic adjuncts is administered. Consistency of the haemodynamic parameters were

observed following PP in gabapentin and clonidine group, but not in the placebo group. This research included study of haemodynamic profile of three groups till initial 35 minutes, the average surgical duration for the procedure in the centre where the study took place. This study also shows that placebo group without clonidine or gabapentin premedication failed to check the rise in serum cortisol following carbon dioxide PP, $p<0.05$. On the other hand gabapentin appeared to check the release of cortisol when compared to clonidine group, $p<0$. The blood glucose profile pre and post PP in three groups was not different statistically, $p<0.05$.

Clonidine, an α-2 adrenoreceptor agonist is absorbed after oral administration and reaches its peak plasma concentration within 60-90 min. It has a half life of 9-12 hours. [7]

Gabapentin was introduced in 1994 as an adjuvant antiepileptic drug. It has found its applications as a broad spectrum analgesic and as a multimodal peri-operative drug.[8] It is extensively distributed in tissue and fluid after oral administration. After a single oral dose of 300 mg, peak plasma concentrations are attained in 2-3hrs. It does not bind to plasma proteins and is not metabolized. It is eliminated unchanged in urine. The elimination half- life after a single oral dose of 200-400 mg is 5-7 hours.[8] Perioperative oral gabapentin is a useful adjunct for the management of postoperative pain that provides analgesia through a different mechanism than opioids and other analgesics thus making it a reasonable addition to a multimodal analgesic treatment plan.[9,10] Gabapentin has been used perioperatively for reducing stress responses in different clinical scenario.[11-14] Gabapentin elevates pain threshold & prevents acute nociceptive and inflammatory pain especially when given before trauma. Several workers have found that 300-1200 mg oral gabapentin given 1 hr before surgical stimulus significantly reduces the incidence of pain and post operative opioid consumption without significant side effects.[15,16] There has been a report of preemptive use of gabapentin in laparoscopic cholecystectomy for its analgesic sparing properties .[17] In our study, oral clonidine 150 mcg or gabapentin 600 mg was given 60 min before planned laparoscopic cholecystectomy.

The effects of anaesthesia and IPPV, reverse Trendelenberg position and, mechanical and endocrine effects of PP produce characteristic haemodynamic response during laparoscopic surgery.[18,19] Hypertension and tachycardia were remarkable during the application of carbon dioxide PP in the placebo group. Patients premedicated with clonidine or gabapentin had more stable haemodynamics in our study. Similar haemodynamic outcomes have been documentated by different authors when they used clonidine as a premedicant with the similar dose.[20-24] But there are reports of using clonidine at the dose up to 5 mcg/kg higher than ours with better and smooth haemodynamic profile. [25]

Laparoscopic surgery has been found to be associated with mimimal stress demonstrated by less release of plasma cortisol when compared to open surgery.[26,27] Premedication with suitable agent like gabapentin or clonidine might thus offer a great advantage upon them. The rise in cortisol level may not be due to the carbon dioxide absorbed during PP as it was targeted to a fixed physiological value in this study (PCO_2 35-40 mm of Hg). In the study by Joris et al it was found that clonidine had no effect on cortisol release .[28] Our study also failed to demonstrate checking its release post PP significantly in clonidine group.The haemodynamic stability in clonidine group might be because of factors like attenuation of sympathoadrenal system, central adrenergic inhibition or suppression of renin and vasopressin release as explained by Joris.[28] Yet there are reports of decreased cortisol release after oral clonidine administration.[29,30] Clonidine premedication has conflicting reports on cortisol level following PP in humans .[28]

The haemodynamic changes parallel the release of endogenous stress hormones like vasopressin, rennin and catecholamines. Hyperglycemia and cortisol release are one of the markers of stress response. The change in haemodynamics and endocrine stress mediators are the result of interplay of different factors like patient, type and method of anaesthesia, surgical technique, duration and extensiveness of tissue trauma.The alterations in endocrine values are not only linked to PP. Laryngoscopy and intubation,ongoing surgery and tissue handling is also responsible for the stress imposed to the patients. The serum glucose values pre and post PP in three groups were not different statistically in our study, $p>0.05$. This showed the stress of PP could not be interpreted in terms of sole serum glucose estimation only. Blood glucose level is closely associated with fasting hours and there had been possibility of inability to synchronize the fasting hours during their waiting for surgery.

Techniques and type of anaesthesia was made similar to all patients in our study. We studied the glucose and cortisol level just before PP and at 10^{th} minutes of PP assuming this initial time period of hormonal study reflects the maximal influence of PP.

Haemodynamic changes associated with PP were first recognized in 1947.[31] This study revealed that peritoneal carbon dioxide insufflation to an intraabdominal pressure of 12 mm Hg causes significant increase in HR, SBP, DBP and MAP in healthy patients. From this point of view gabapentin succeeded to maintain its superiority

over clonidine or placebo group in this cohort study to lessen stress of PP. The mechanism of gabapentin in attenuating haemodynamic and endocrine response remains unknown. This warrants further investigations. We speculate that as gabapentin inhibits membrane voltage gated calcium channels, it is possible that it may have an action similar to that of calcium channel blockers.[32]

Haemodynamic change is anticipated if the intraperitoneal pressure is more than 16 mm Hg and the change is expected to be minimal with the pressure less than 14 mm of Hg.[33] PP causes caval compression, pooling of blood in the peripheral circulation leading to decreased preload.[34,35] The increase in blood pressure, HR during laparoscopic surgery has been documentated due to release of catecholamines,[36] renin and vasopressin.[36,37] PP causes activation of sympathetic system, mechanical compressive effect and surgical stress leading to rise in serum renin level.[38,39]

This current study used 600 mg of oral gabapentin without any serious side effects like delayed emergence in patients enrolled. One patient in gabapentin and three in clonidine group had faced HR below 40- 45/ min intraoperatively and were treated with inj atropine. In the study conducted by Pouttu J et al also they had encountered increased incidence of bradycardia in patients premedicated with clonidine.[40]

This study carried out the test of serum cortisol and glucose before PP and following PP at one single point of time due to financial constraints. It would have been better if the tests could have been done at different time points of PP including basal cortisol and glucose level prior to premedication, during and after laryngoscopy/ intubation. This study observed haemodynamic stability in patients premedicated with oral gabapentin which was correlated by decrease in cortisol release post PP. This study is not in position to clarify whether the stress hormone release continued to diminish beyond the 10th minute of PP in respective groups. This has become a matter of interest for further research and investigations how gabapentin influence on other stress hormones.

CONCLUSIONS

Oral premedication with 600 mg of gabapentin or clonidine 150 mcg an hour prior to routine laparoscopic cholecystectomy offers stable haemodynamic profile which parallels to the attenuation of cortisol release. Gabapentin premedication reduces serum cortisol level when taken as a stress marker of PP in laparoscopic cholecystectomy.

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